IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH) **DEMAND FOR JURY TRIAL**
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC., Plaintiff/Counter Defendants.	

EXHIBIT 14C

NIPPON SHINYAKU CO., LTD. AND NS PHARMA, INC.'S MOTION *IN LIMINE* NO. 3 TO PRECLUDE MENTION OF *INTER PARTES* REVIEW PROCEEDINGS INVOLVING THE PATENTS

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NIPPON SHINYAKU CO., LTD. AND NS PHARMA, INC.'S MOTION IN LIMINE NO. 3 TO PRECLUDE MENTION OF *INTER PARTES* REVIEW PROCEEDINGS INVOLVING THE NS PATENTS

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Dated: April 19, 2024

NS respectfully requests that the Court preclude Sarepta and UWA from presenting any testimony or evidence regarding or mentioning *inter partes* review proceedings ("IPRs") involving the NS Patents in the jury trial portion of this case.[1] Like many defendants, Sarepta seeks to rely upon the preliminary institution of the IPRs to allegedly "reinforce" its argument that the NS Patents are invalid (D.I. 427-1, ¶ 619) and support its arguments against willful infringement. Courts routinely express skepticism at such relevancy claims and exclude evidence of IPRs, as this Court recently did. *See Sight Sci., Inc. v. Ivantis, Inc.*, C.A. No. 21-1317-JLH-SRF, D.I. 430 at 4. Allowing mention of now-terminated IPRs to the jury would be unfairly prejudicial and confusing.

Sarepta's misconduct in procuring the IPRs at-issue only heightens the need for exclusion. As the Federal Circuit held, Sarepta's filing of the IPR petitions "contravened the plain language of the forum selection clause" and breached the parties' Mutual Confidentiality Agreement. *Nippon Shinyaku Co. v. Sarepta Therapeutics, Inc.*, 25 F.4th 998, 1006 (Fed. Cir. 2022). Allowing Sarepta to now leverage those IPRs—which never should have been brought—against Nippon Shinyaku would be fundamentally unfair. The Court should not endorse Sarepta's attempt to further exploit the ill-gotten fruits of its breach.

A. The Improperly Filed IPRs are Irrelevant.

Sarepta filed the IPRs regarding the NS Patents in contravention of an "unambiguous" forum selection clause it had agreed to. *Nippon Shinyaku*, 25 F.4th at 1006. For this reason alone, it is improper for Sarepta to now attempt to benefit from its contractual breach by relying on its wrongly filed IPRs at trial.

But even setting aside the impropriety of Sarepta's filings, its intended reliance on the IPRs is irrelevant to the issues the jury will need to decide. Sarepta does not cite the IPRs to highlight

[1] The IPRs are relevant to NS's breach of contract claim which the parties have agreed to try to the Court, and, thus, the instant motion pertains only to the jury trial portion of this case.

particular factual assertions made by Nippon Shinyaku about the NS Patents, prior art, or state of the art. Rather, it seeks to bolster the opinions of its technical expert, Dr. Dowdy, using the PTAB's ***institution decisions***. *See, e.g.*, D.I. 427-1 (Dowdy Opening Report) ¶ 621; D.I. 427-2 (Dowdy Rebuttal Report) ¶¶ 485, 489. This invites confusion and unfair prejudice.

Although the PTAB instituted the IPRs, Judge Noreika ordered Sarepta to withdraw these IPRs, which it did before any further activity. *See* D.I. 111 (granting injunction and requiring withdrawal of improperly-filed IPRs). Thus, the PTAB never reached a final written decision, nor did any evidentiary development and/or ensuing appeal occur. The lack of finality of the PTAB's institution decision demonstrates the IPRs' lack of relevancy and weighs strongly against admission. *Andover Healthcare v. 3M*, 2016 WL 6404111, at *2 (D. Del. Oct. 27, 2016) (noting that without "a final decision on validity . . . the minimal (if any) probative value of the PTAB's decision is far outweighed by the risk of jury confusion and unfair prejudice"); *Personalized User Model, L.L.P. v. Google Inc.*, 2014 WL 807736, at *3 (D. Del. Feb. 27, 2014) (holding similar).

Moreover, because the IPRs' standards of proof and procedures through institution greatly differ, Sarepta's intended reliance on PTAB's preliminary decisions is irrelevant and misleading. The IPR institution standard (a "reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition," 35 U.S.C. § 314(a)) is lower than a petitioner's burden to ultimately prevail in an IPR, and far lower than Sarepta's burden at trial to show invalidity by clear and convincing evidence. That the PTAB instituted based on this much lower standard is of no relevance to showing that Sarepta's infringement was not willful. *IOENGINE, LLC v. PayPal Holdings, Inc.*, 2022 WL 2800911, at *2 (D. Del. June 27, 2022) (Bryson, J.) ("With regard to willful infringement, I am skeptical that evidence of IPRs filed after this litigation began is particularly probative of willfulness."); *SSL Servs., LLC v. Citrix Sys., Inc.*, 769 F.3d 1073, 1092-

93 (Fed. Cir. 2014) ("warn[ing] of the limited value of actions by the PT[AB] to establish a good faith belief of invalidity" for willfulness and upholding district court's determination that "probative value of unfinished agency proceedings was substantially outweighed by the risk of unfair prejudice") . This difference in evidentiary standards weighs strongly against allowing the jury to hear about decisions in instituted–now terminated–non-final IPRs. *IOENGINE*, 2022 WL 2800911, at *2 (different standards of proof create substantial risk of undue prejudice from allowing evidence regarding PTAB proceeding); *Integra LifeSciences Corp. v. Hyperbranch Med. Tech., Inc.*, 2018 WL 2186677, at *1 (D. Del. May 11, 2018) (same); *see also SRI Int'l Inc. v. Internet Sec. Sys., Inc.*, 647 F. Supp. 2d 323, 356 (D. Del. 2009) (same citing "overwhelming possibility of jury confusion").

B. Any Probative Value is Substantially Outweighed by Unfair Prejudice.

The Federal Circuit has explained that if evidence of non-final PTAB proceedings is introduced, "the risk of jury confusion" is "high." *Callaway Golf Co. v. Asushnet Co.*, 576 F.3d 1331, 1343 (Fed. Cir. 2009). Thus, "the vast majority of courts" have found that any probative value of evidence relating to reexamination or IPR proceedings is outweighed by the risk of unfair prejudice, risk of jury confusion, or waste of time. *IA Labs CA, LLC v. Nintendo Co.*, 857 F. Supp. 2d 550, 552 (D. Md. 2012). The reason for this is simple: presentation of IPR evidence would only "create[] a distracting side show" that would "confuse[] the jury." *SynQor, Inc. v. Artesyn Techs., Inc.*, 2011 WL 3625036, at *12 (E.D. Tex. Aug. 17, 2011).

Indeed, "telling the jury that the patent has been called into question by the Patent Office may significantly influence the jury's application of the presumption of validity and significantly prejudice [Plaintiff]." *Amphenol T & M Antennas v. Centurion Int'l, Inc.*, 2002 WL 32373639, at *2 (N.D. Ill. Jan. 17, 2002). Thus, courts routinely exclude evidence of PTAB proceedings. *Sight Sci.*, D.I. 430 at 4; *IOENGINE*, 2022 WL 2800911, at *1; *Integra*, 2018 WL 2186677, at *1.

April 19, 2024

Respectfully submitted,

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH) [redacted]
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	

SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S OPPOSITION TO PLAINTIFF/COUNTER-DEFENDANTS' MOTION *IN LIMINE* NO. 3 TO EXCLUDE MENTION OF *INTER PARTES* REVIEW PROCEEDINGS INVOLVING THE NS PATENTS

Before NS filed this lawsuit, Sarepta had already filed *inter partes* review ("IPR") petitions challenging each of the NS Patents asserted in this case as obvious under 35 U.S.C. § 103. *See, e.g.*, Ex. A. The NS Patents are directed to antisense oligonucleotides ("ASOs") that induce exon skipping that: (1) target positions (+36+60) of exon 53 of the human dystrophin pre-mRNA and (2) have certain chemical features. The two prior art references asserted by Sarepta both in the IPRs and this litigation[1] show: (1) an ASO targeting positions (+35+59) of exon 53—just one position shifted from the claimed ASO and (2) the chemical features of the claimed ASO. The USPTO instituted all seven IPRs, finding a reasonable likelihood of invalidity for each NS Patent. That the IPRs later were withdrawn (after the Federal Circuit reversed Judge Stark's ruling on NS's breach of contract claim) does not undermine Sarepta's reasonable, good faith, pre-suit belief in the invalidity of the NS Patents as evidenced by its substantial investment in filing the IPRs.

Although NS put Sarepta's state of mind at issue by alleging that Sarepta willfully infringed NS's Patents, it now asks the Court to preclude Sarepta from presenting evidence to rebut that charge. Specifically, NS seeks to preclude Sarepta from presenting testimony or evidence that before NS brought this suit, Sarepta had filed IPRs against all seven NS Patents asserted in this case based on Sarepta's belief that the NS Patents are invalid.[2] The jury is entitled to hear about the IPRs—which involved the same prior art references Sarepta relies on now to challenge the same NS Patents as obvious—because they are relevant for at least two independent reasons.

[1] Sarepta relies on two references in its § 103 argument: (1) Popplewell et al., Neuromuscul. Disord. (2010) 20:102–110 ("Popplewell 2010"); and Sazani et al., Int'l J. of Toxicology (2010) 29(2):143–156 ("Sazani 2010"). These are the same two references asserted in the IPR petitions.

[2] Joseph Zenkus, Sarepta's Sr. Vice President, Business Development and Strategic Alliances testified at deposition that Sarepta filed the IPRs against the NS Patents because of Sarepta's belief that the patents are unpatentable. Ex. B, Zenkus Dep. Tr. at 227:4-23; [redacted]

First, the IPRs are relevant to Sarepta's defense to NS's charge of willfulness as evidence of Sarepta's reasonable, good faith belief that the NS Patents are invalid. *See Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 136 S. Ct. 1923, 1933 (2016). This is similar to how an opinion of counsel evidences a lack of willfulness. *See, e.g.*, *Greatbatch Ltd. v. AVX Corp.*, C.A. No. 13-723-LPS, 2016 WL 7217625, at *4 (D. Del. Dec. 13, 2016) (finding no willful infringement as a matter of law in view of reliance on invalidity opinion of counsel). The Court has discretion to permit Sarepta to rely on testimony and evidence regarding the IPRs at least for its defense to willfulness. *See, e.g.*, *EIS Inc. v. IntiHealth Ger GmbH*, No. 19-1227-GBW, D.I. 656 (D. Del. Sept. 8, 2023) (confirming denial of motion *in limine* seeking to preclude IPR proceedings) (Ex. C); *Bos. Sci. Corp. v. Cook Med. LLC*, No. 1:17-cv-03448-JRS-MJD, 2023 WL 2411277, at *1 (S.D. Ind. Feb. 2, 2023) (allowing defendant to point to IPRs in support of defense to willfulness); *Hillman Grp., Inc. v. KeyMe LLC*, No. 2:19-CV-00209-JRG, 2021 WL 1248180, at *3 (E.D. Tex. Mar. 30, 2021) (noting IPRs are relevant to willfulness and allowing reference to "statements to or decisions from the 'Patent Office'"); *Finjan, Inc. v. Cisco Sys. Inc.*, No. 17-cv-00072-BLF, 2020 WL 13180008, at *10 (N.D. Cal. June 5, 2020) (denying motion to exclude post-grant proceedings where the court was "persuaded that the strength of the Asserted Patents is relevant to Cisco's good faith belief as to the validity of the Asserted Patents – and is therefore relevant to ***willfulness***").

Second, to the extent that NS argues to the jury that the USPTO previously considered references that are either the same or allegedly cumulative to those Sarepta relies on for obviousness, it is only fair that Sarepta be permitted to tell the jury that, upon a second look, the USPTO found that there was a reasonable likelihood that these references would result in finding the NS Patents unpatentable. In other words, if NS argues that the USPTO granted the NS Patents despite having before it either the same or cumulative prior references to those relied on by Sarepta,

NS will have opened the door to the IPRs and "cannot expect to enter such evidence on their behalf and then argue that [Sarepta] cannot do so." *Dentsply Sirona Inc. v. Edge Endo, LLC*, No. 1:17-CV-1041-JFB-SCY, 2020 WL 6392764, at *5 (D.N.M. Nov. 2, 2020); *cf. Andover Healthcare, Inc. v. 3M Co.*, No. 13-843-LPS, 2016 WL 6404111, at *2 (D. Del. Oct. 27, 2016) (noting court would reevaluate grant of motion to exclude reference to IPR non-institution decision should the moving party attempt to prove that the USPTO did not consider the prior art from the IPR petition). NS cannot open the door in that way and then shut it to prevent Sarepta from responding.

The cases cited by NS are inapposite. They do not address willfulness,[3] involved unsuccessful IPRs where institution was denied[4] or unsuccessful reexamination proceedings where invalidity arguments were rejected,[5] and/or are related to USPTO proceedings initiated *after* suit had been filed[6]—despite the fact that "culpability is generally measured against the knowledge of the actor ***at the time*** of the challenged conduct." *Halo Elecs.*, 136 S. Ct. at 1933 (emphasis added).[7] The Court should deny NS's motion.

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[3] *See Personalized User Model, L.L.P. v. Google Inc.*, 2014 WL 807736 (D. Del. Feb. 27, 2014) (does not address willfulness); *Andover Healthcare, Inc. v. 3M Co.*, 2016 WL 6404111 (D. Del. Oct. 27, 2016) (same); *SRI Int'l Inc. v. Internet Sec. Sys., Inc.*, 647 F. Supp. 2d 323 (D. Del. 2009) (same); *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331 (Fed. Cir. 2009) (same); *IA Labs CA, LLC v. Nintendo Co.*, 857 F. Supp. 2d 550 (D. Md. 2012) (same); *SynQor, Inc. v. Artesyn Techs., Inc.*, 2011 WL 3625036 (E.D. Tex. Aug. 17, 2011) (same); *Amphenol T & M Antennas, Inc. v. Centurion Int'l, Inc.*, 2002 WL 32373639 (N.D. Ill. Jan. 17, 2002) (same).

[4] *SSL Servs., LLC v. Citrix Sys., Inc.*, 769 F.3d 1073, 1091 (Fed. Cir. 2014).

[5] *Sight Sci., Inc. v. Ivantis, Inc.*, C.A. No. 21-1317-JLH-SRF, D.I. 430, at 4 (D. Del. Apr. 2, 2024), D.I. 422, at 1 (D. Del. Mar. 25, 2024).

[6] *See IOENGINE, LLC v. PayPal Holdings, Inc.*, No. 18-452-WCB, 2022 WL 2800911, at *2 (D. Del. June 27, 2022) ("With regard to willful infringement, I am skeptical that evidence of IPRs filed after this litigation began is particularly probative of willfulness.")

[7] In one case cited by NS, the court excluded all information relating to pre-trial rulings including its claim construction and IPR proceedings, specifically noting that its ruling extended to the IPR claim construction and its impact on the court's claim construction. *Integra LifeSciences Corp. v. Hyperbranch Med. Tech., Inc.*, 2018 WL 2186677, at *1 (D. Del. May 11, 2018). Here, neither the Court nor the PTAB construed any terms from the remaining NS Patents.

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April 25, 2024

CERTIFICATE OF SERVICE

I hereby certify that on April 25, 2024, copies of the foregoing were caused to be served upon the following in the manner indicated:

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EXHIBIT A

Filed: June 21, 2021

Filed on behalf of: Sarepta Therapeutics, Inc.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAREPTA THERAPEUTICS, INC.
Petitioner

v.

NIPPON SHINYAKU CO., LTD.
&
NATIONAL CENTER OF NEUROLOGY AND PSYCHIATRY
Patent Owners

Case No. IPR2021-01135
Patent No. 10,385,092

PETITION FOR *INTER PARTES* REVIEW

EXHIBIT LIST

Exhibit	Description
EX1001	U.S. Patent No. 10,385,092
EX1002	PCT Patent Application No. PCT/JP2011/070318 (published as WO2012029986)
EX1003	Japanese Provisional Application No. 2010-196032
EX1004	Certified translation of Japanese Provisional Application No. 2010-196032
EX1005	Certified translation of PCT Application No. PCT/JP2011/070318
EX1006	Affidavit (translation declaration Japanese Provisional Application No. 2010-196032)
EX1007	Affidavit (translation of PCT Application No. PCT/JP2011/070318)
EX1008	Reserved
EX1009	Reserved
EX1010	Reserved
EX1011	Excerpts of file history of U.S. Patent No. 9,708,361
EX1012	Excerpts of file history of U.S. Patent No. 10,385,092
EX1013	Reserved
EX1014	Reserved
EX1015	Reserved
EX1016	Reserved
EX1017	Reserved
EX1018	Reserved
EX1019	Reserved

Exhibit	Description
EX1020	Reserved
EX1021	Popplewell et al., "Comparative Analysis of Antisense Oligonucleotide Sequences Targeting Exon 53 of the Human DMD Gene: Implications for Future Clinical Trials," *Neuromuscul. Disord.* (2010) 20:102–110
EX1022	Sazani et al., "Safety Pharmacology and Genotoxicity Evaluation of AVI-4658," *Int. J. Toxicol.* (2010) 29(2):143–156
EX1023	U.S. Patent Application Publication No. 2010/0168212
EX1024	U.S. Patent Application Publication No. 2010/0130591
EX1025	U.S. Patent Application Publication No. 2013/0109091
EX1026	U.S. Patent Application Publication No. 2012/0190728
EX1027	Bushby et al., "Diagnosis and Management of Duchenne Muscular Dystrophy, Part 1: Diagnosis, and Pharmacological and Psychosocial Management," *Lancet Neurol.* (2010) 9(1): 77–93
EX1028	Kinali et al., "Local Restoration of Dystrophin Expression with the Morpholino Oligomer AVI-4658 in Duchenne Muscular Dystrophy: A Single-Blind, Placebo-Controlled, Dose-Escalation, Proof-of-Concept Study," *Lancet Neurol.* (2009) 8(10): 918–928
EX1029	Hoffman et al., "Skipping Toward Personalized Molecular Medicine," *N. Engl. J. Med.* (2007) 357(26): 2719–2722
EX1030	Wilton et al., "Exon Skipping and Duchenne Muscular Dystrophy: Hope, Hype and How Feasible?" *Neurol. India* (2008) 56(3): 254–262
EX1031	Arechavala-Gomeza et al., "Comparative Analysis of Antisense Oligonucleotide Sequences for Targeted Skipping of Exon 51 During Dystrophin Pre-mRNA Splicing in Human Muscle," *Hum. Gene. Ther.* (2007) 18(9): 798–810
EX1032	Ginjaar et al., "Dystrophin Nonsense Mutation Induces Different Levels of Exon 29 Skipping and Leads to Variable Phenotypes Within One BMD Family," *Eur. J. Hum. Genet.* (2000) 8(10): 793–796

Exhibit	Description
EX1033	Wilton et al., "Antisense Oligonucleotides, Exon Skipping and the Dystrophin Gene Transcript," *Acta Myol.* (2005) 24(3): 222–229
EX1034	Reserved
EX1035	Wilton et al., "Antisense Oligonucleotide-Induced Exon Skipping Across the Human Dystrophin Gene Transcript," *Mol. Ther.* (2007) 15(7): 1288–1296
EX1036	Muntoni et al., "The Development of Antisense Oligonucleotide Therapies for Duchenne Muscular Dystrophy: Report on a TREAT-NMD Workshop Hosted by the European Medicines Agency (EMA), on September 25th 2009," *Neuromuscul. Disord.* (2010) 20(5): 355–362
EX1037	van Deutekom et al., "Local Dystrophin Restoration with Antisense Oligonucleotide PRO051," *N. Engl. J. Med.* (2007) 357(26): 2677–2686
EX1038	Goemans et al., "Systemic Administration of PRO051 in Duchenne's Muscular Dystrophy," *N. Engl. J. Med.* (2011) 364(16): 1513–1522
EX1039	Cirak et al., "Exon Skipping and Dystrophin Restoration in Patients with Duchenne Muscular Dystrophy After Systemic Phosphorodiamidate Morpholino Oligomer Treatment: An Open-Label, Phase 2, Dose-Escalation Study," *Lancet* (2011) 378(9791): 595–605
EX1040	Nakamura et al., "Exon-Skipping Therapy for Duchenne Muscular Dystrophy," *Neuropathology* (2009) 29(4): 494–501
EX1041	Yokota et al., "A Renaissance for Antisense Oligonucleotide Drugs in Neurology," *Arch. Neurol.* (2009) 66(1): 32–38
EX1042	Aartsma-Rus et al., "Guidelines for Antisense Oligonucleotide Design and Insight into Splice-Modulating Mechanisms," *Mol. Ther.* (2009) 17(3): 548–553
EX1043	Aartsma-Rus et al., "Less is More: Therapeutic Exon Skipping for Duchenne Muscular Dystrophy," *Lancet Neurol.* (2009) 8(10): 873–875
EX1044	Chan et al., "Antisense Oligonucleotides: From Design to Therapeutic Application," *Clin. Exp. Pharmacol. Physiol.* (2006) 33(5-6): 533–540

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EX1046	Adams et al., "Antisense Oligonucleotide Induced Exon Skipping and the Dystrophin Gene Transcript: Cocktails and Chemistries," *BMC Mol. Biol.* (2007) 8:57
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EX1049	PCT Patent Application Publication No. WO 2004/083432
EX1050	PCT Patent Application Publication No. WO 2006/000057
EX1051	U.S. Patent Application Publication No. 2007/0082861
EX1052	Popplewell et al., "Design of Phosphorodiamidate Morpholino Oligomers (PMOs) for the Induction of Exon Skipping of the Human DMD Gene," *Mol. Ther.* (2009) 17(3): 554–561
EX1053	Moulton et al., "Gene Knockdowns in Adult Animals: PPMOs and Vivo-Morpholinos," *Molecules* (2009) 14(3): 1304–1323
EX1054	PCT Patent Application Publication No. WO 2011/057350
EX1055	Summerton, "Morpholino Antisense Oligomers: The Case for an RNase H-independent Structural Type," *Biochim. Biophys. Acta* (1999) 1489(1): 141–158
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EX1057	Aartsma-Rus et al., "Antisense-Mediated Exon Slipping: A Versatile Tool with Therapeutic and Research Applications," *RNA* (2007) 13(10): 1609–1624

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EX1058	Trollet et al., "Gene Therapy for Muscular Dystrophy: Current Progress and Future Prospects," *Expert Opin. Biol. Ther.* (2009) 9(7): 849–866
EX1059	"Prosensa and GlaxoSmithKline Initiate Development of Four Additional Products under Existing Alliance in Duchenne Muscular Dystrophy; Broadened Program Marks Key Inflexion in Prosensa's Progress to a Fully Integrated Specialty-Pharma Company," *Business Wire* (June 23, 2010)
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GLOSSARY

AO	Antisense oligomer
BMD	Becker muscular dystrophy
DMD	Duchenne muscular dystrophy
exon 53	the 53rd exon of the human dystrophin (or *DMD*) gene
FDA	U.S. Food and Drug Administration
IPR	*Inter partes* review
Italicized text	Emphasis added unless otherwise indicated
NS or Patent Owners	Nippon Shinyaku Co., Ltd. National Center of Neurology and Psychiatry
Sarepta or Petitioner	Sarepta Therapeutics, Inc.
PMO	phosphorodiamidate morpholino oligomer
2'-OMePS	phosphorothioate-linked 2'-O-methyl oligomer
TEG	triethylene glycol
POSA	Person of ordinary skill in the art
Japanese Application	Japanese Priority Application No. 2010-196032
USPTO or Office	U.S. Patent and Trademark Office
'092 patent	U.S. Patent No. 10,385,092
'361 patent	U.S. Patent No. 9,708,361
'461 patent	U.S. Patent No. 10,407,461
'106 patent	U.S. Patent No. 10,487,106
'741 patent	U.S. Patent No. 10,647,741
'217 patent	U.S. Patent No. 10,662,217

'322 patent	U.S. Patent No. 10,683,322

I. Statement of Precise Relief Requested and Reasons Therefor (37 C.F.R. § 42.22(A))

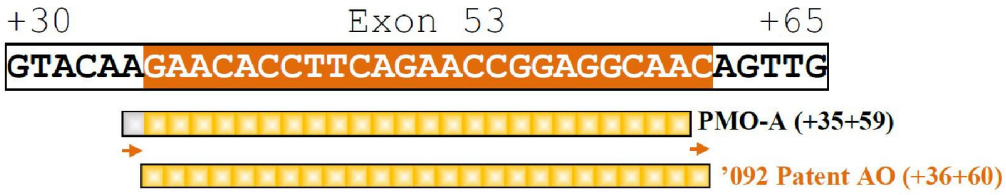
Sarepta hereby submits this petition for *inter partes* review ("Petition") seeking cancellation of claims 1–3 of U.S. Patent No. 10,385,092 ("the '092 patent") (EX1001), assigned to Nippon Shinyaku Co., Ltd. and National Center of Neurology and Psychiatry (collectively, "NS" or "Patent Owners"). The challenged claims are unpatentable under 35 U.S.C. § 103(a). This Petition is supported by the declaration of Dr. David R. Corey, an expert in the design and evaluation of antisense oligomers for therapeutic purposes. This Petition is being filed concurrently with Petitions for related U.S. Patent Nos. 9,708,361 ("the '361 patent"), 10,487,106 ("the '106 patent"), 10,407,461 ("the '461 patent"), 10,647,741 ("the '741 patent"), 10,662,217 ("the '217 patent"), and 10,683,322 ("the '322 patent"), all of which have claims substantially similar to the claims challenged in this Petition.

II. Introduction

The challenged claims encompass antisense oligomers ("AOs") that induce skipping of exon 53 of the human dystrophin pre-mRNA and consist of a "25-mer oligomer that is 100% complementary" to positions 36 to 60 (+36+60) of exon 53 of the human dystrophin pre-mRNA.

The challenged claims are obvious over the prior art. By August 31, 2011, AO-induced exon skipping was a promising therapeutic approach for restoring

functional dystrophin in DMD patients, with proof-of-principle clinical trials providing encouraging results. Moreover, scientists had identified numerous AOs that effectively skipped exon 53: testing of AOs by multiple research groups had identified positions 30 to 65 (+30+65) within exon 53 as a hotspot target region for AOs causing exon 53 skipping. One of the AOs binding to this hotspot (PMO-A), described in the prior art as a "viable" candidate for upcoming exon 53 clinical trials, targeted and was perfectly complementary to positions 35 to 59 of exon 53 (+35+59)—just one position shifted from the claimed AO.



A POSA would have been motivated to generate an AO targeting the +36+60 sequence of exon 53 as part of a conventional screen to optimize the prior art AOs. Such screens were well-established and routine by August 31, 2011. Further, a POSA would have reasonably expected that an AO targeting the +36+60 sequence of exon 53 would successfully induce skipping of exon 53, as numerous prior art AOs targeting this region had already exhibited skipping, including PMO-A targeting positions +35+59 of exon 53. Thus, the claims of the '092 patent encompass nothing more than the application of routine techniques for optimizing the sequences of AOs for exon skipping that were well known to a POSA before August 31, 2011.

The objective evidence supports a conclusion of obviousness. Indeed, the claimed subject matter was published independently within months of the effective filing date for the '092 patent. Moreover, while NS secured allowance of a parent application to the '092 patent—which is also directed to an AO targeting the +36+60 sequence of exon 53—by alleging unexpected results, those results are illusory. As described below, a direct comparison disclosed in NS's own patent specification, overlooked by the Examiner, shows that an AO targeting the claimed +36+60 sequence had similar (and perhaps less) skipping efficacy than a prior art AO targeting the +35+59 sequence of exon 53.

Because challenged claims 1–3 offer nothing inventive over what was well known as of August 31, 2011, Sarepta requests *inter partes* review.

Notably, the '092 patent is one of several related patents obtained by NS with substantially similar claims. For instance, the '361, '106, and '461 patents are directed to a 25-mer targeting the same +36+60 sequence of exon 53 recited in the challenged claims. The '741 and '217 patents are directed to methods of administering AOs targeting the +36+60 sequence. The '322 patent is directed to methods of making AOs targeting the +36+60 sequence. During prosecution of the '092 patent, NS filed terminal disclaimers over the '361 patent, as well as over the applications leading to the '106 and '461 patents. Petitions challenging the '361, '106, '461, '741, '217, and '322 patents are being filed concurrently.

III. Grounds for Standing

Petitioner certifies that the '092 patent is available for IPR and that Petitioner is not barred or estopped from requesting review on the ground identified. (EX1012, 4–5 (March 20, 2019, Application Data Sheet listing priority chain and declining to designate as a transition application); EX1001, 1:6–15, title page, items (63) & (30).)

IV. Identification of Challenge

Sarepta requests that claims 1–3 of the '092 patent be found unpatentable and cancelled in view of the following references:

Reference 1: Popplewell et al., *Neuromuscul. Disord.* (2010) 20:102–110 ("Popplewell") (EX1021), published in February 2010. Popplewell is prior art to the '092 patent under 35 U.S.C. § 102(b). *See* EX1088 (declaration confirming public accessibility of Popplewell prior to August 31, 2011).

Reference 2: Sazani et al., *Int'l J. of Toxicology* (2010) 29(2):143–156 ("Sazani") (EX1022), published in March 2010. Sazani is prior art to the '092 patent under 35 U.S.C. § 102(b). *See* EX1088 (declaration confirming public accessibility of Sazani prior to August 31, 2011).

The specific ground is:

Ground	Claims	Description
1	1–3	Obvious under 35 U.S.C. § 103(a) over Popplewell and Sazani

V. The Alleged Invention of the '092 Patent

The '092 patent issued on August 20, 2019, from U.S. Application No. 16/359,213, and claims priority to PCT/JP2011/070318 (EX1002), filed August 31, 2011, and Japanese Provisional Application No. 2010-196032 (EX1003), filed on September 1, 2010. (EX1095, ¶¶78–80.) Certified English translations of Japanese Provisional Application No. 2010-196032 (EX1004) and PCT/JP2011/070318 (EX1005), along with accompanying translation declarations (EX1006; EX1007) are submitted with this Petition. The '092 patent is a grandchild of the '361 patent, and a Petition for the '361 patent is being filed concurrently.

The '092 patent is entitled "Antisense Nucleic Acids." (EX1001, title page, item (54); *see* EX1095, ¶¶88–91.) It states that the alleged invention "relates to an antisense oligomer which causes skipping of exon 53 in the human dystrophin gene, and a pharmaceutical composition comprising the oligomer." (EX1001, 1:28–31.) The specification describes the "present invention" as an AO which induces skipping of exon 53, consisting of an oligomer sequence complementary to one of 36 listed sequences within the 31st and 58th nucleotides of exon 53.[1] (*Id.*, 3:23–41; *see also*

[1] Unless indicated otherwise, target regions of exon 53 discussed herein are counted from the 5'-end of exon 53.

id., Table 1 (listing AOs of SEQ ID NOs. 2–37).) Additional AOs complementary to exon 53 are provided in Tables 2 and 7, including the AO identified as H53_36-60, which targets the 36th to 60th nucleotides of exon 53 of the human dystrophin pre-mRNA. (*Id.*, Table 2, Table 7 (listing SEQ ID NOs. 49–123).)

The patent contains no clinical data and no studies in humans.

A. The Challenged Claims

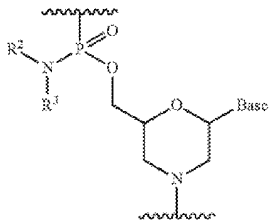
The '092 patent contains three claims, all of which are independent claims. Claim 1 recites as follows:

> 1. A phosphorodiamidate morpholino oligomer (PMO) antisense oligomer that causes skipping of the 53rd exon in a human dystrophin pre-mRNA,
>
> consisting of a 25-mer oligomer that is 100% complementary to the 36th to the 60th nucleotides from the 5' end of the 53rd exon in said human dystrophin pre-mRNA,
>
> wherein the 53rd exon in said human dystrophin pre-mRNA consists of a nucleotide sequence corresponding to SEQ ID NO: 1, and
>
> wherein said PMO antisense oligomer hybridizes to said pre-mRNA with Watson-Crick base pairing under physiological conditions.

(EX1001, claim 1.) SEQ ID NO: 1 is identical to exon 53 of the human dystrophin gene, the sequence of which was known in the prior art before the '092 patent was filed. (EX1001, 6:45–49; EX1095, ¶81.)

Independent claim 2 is identical to claim 1, except it additionally specifies the structure of the PMO monomer:

> wherein each phosphorodiamidate morpholino monomer of said PMO antisense oligomer has the formula:

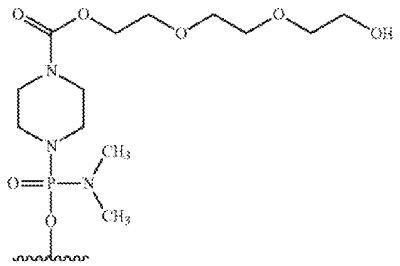


> wherein each of R^2 and R^3 represents a methyl; and
>
> wherein Base is a nucleobase selected from the group consisting of cytosine, thymine, adenine, and guanine.

(EX1001, claim 2; EX1095, ¶82.)

Independent claim 3 is identical to claim 2 except it additionally specifies the structure of the 5'-end group:

> wherein the 5' end of said PMO antisense oligomer has the formula:



(EX1001, claim 3; EX1095, ¶83.)

B. The Effective Filing Date of the '092 Patent

Each of the challenged claims of the '092 patent recites a 25-mer AO that is 100% complementary to positions +36+60 of exon 53. However, the Japanese Application did not disclose an AO targeting positions +36+60 of exon 53.[2] (EX1095, ¶¶84–85.) Instead, an AO targeting positions +36+60 of exon 53 was first disclosed as H53_36-60 in Table 7 of the PCT application filed on August 31, 2011. (EX1095, ¶¶86–87.) As such, the claims of the '092 patent are not entitled to the

[2] The Japanese Application disclosed only the AOs listed in Table 1 and certain AOs listed in Table 2. (EX1004.) In the PCT application filed a year later, NS added the AOs listed in Table 7, including H53_36-60, as well as the remaining AOs listed in Table 2 (PMO NOs. 13–16). (EX1005.) NS's PCT application also included for the first time Examples 1–12, Comparative Examples 1–3, and Test Examples 3–7. (*Id.*)

September 1, 2010, provisional filing date. *In re Wertheim*, 541 F.2d 257, 261 (C.C.P.A. 1976).

NS conceded as much during prosecution of the '092 patent. During prosecution, NS added new claims directed to AOs that are 100% complementary to the 36th to 60th sequence in exon 53. As support for this amendment, NS cited, *inter alia*, to new matter added when the PCT application was filed (EX1012, 21 (citing Table 7).)

Regardless, the references relied upon for the sole ground of unpatentability qualify as prior art under pre-AIA § 102(b). NS's Japanese Application filed in 2010 does not constitute an "application for patent in the United States" under pre-AIA § 102(b). *See* M.P.E.P. § 2152.01 ("[T]he one-year grace period in pre-AIA 35 U.S.C. 102(b) is measured from only the filing date of the earliest application filed in the United States (directly or through the PCT)."). Because the asserted references were publicly available more than one year prior to August 31, 2011, the date of the first patent application in the United States, they are prior art under pre-AIA § 102(b).

C. Summary of Relevant Prosecution History of the '092 Patent

Petitioner summarizes herein the portions of the prosecution history most relevant to the ground of unpatentability set forth in this Petition. The application which matured into the '092 patent was originally filed with claims directed to AOs

complementary to two target regions: the 32nd to 56th nucleotides and the 36th to 56th nucleotides of exon 53 in human dystrophin pre-mRNA. (EX1012, 14–15.) NS later amended the claims to focus on the 36th to 60th nucleotides of exon 53 and requested an interview with the Examiner. (EX1012, 19–20.) Based on an interview summary dated June 4, 2019, the parties discussed "potential amendments to av[o]id Statutory Double patenting concerns" and "the support for claims where it was agreed that there was adequate support in the specification for the claims." (EX1012, 23.)

After the interview, terminal disclaimers were filed over U.S. Application Nos. 16/364,451 (issued as the '461 patent) and 16/369,427 (issued as the '106 patent), and the '361 patent. (EX1012, 25–28.)

A Notice of Allowance issued thereafter and included an Examiner's Amendment to amend the claims as discussed during the interview. (EX1012, 29–37.)

D. Summary of Relevant Prosecution History of the '361 Patent

Petitioner also summarizes herein the relevant portions of the prosecution history of the '361 patent, which is the grandparent of the '092 patent and is also directed to AOs targeting the +36+60 sequence of exon 53. The Office appears to have relied on the substantive examination of the '361 patent—during which the applicant secured allowance by alleging unexpectedly superior properties—in

allowing the claims of the '092 patent, as no rejections were made in view of the prior art during prosecution of the '092 patent.

The application that matured into the '361 patent was originally filed with claims directed to AOs complementary to two target regions: the 32nd to 56th nucleotides and the 36th to 56th nucleotides of exon 53. (EX1011, 21.) In a second preliminary amendment, NS amended the claims to recite 13 different target regions, including the 36th to 60th nucleotides of exon 53. (EX1011, 24–27.) NS stated that "[s]upport for the amendments can be found at least from (1) the original claims of the PCT application, and (2) TEST EXAMPLE 7 and Table 7 of the Specification." (*Id.*)

In a Non-Final Office Action, the Office rejected the amended claims as unpatentable under § 103 over US20100168212 ("the '212 Publication") (EX1023) and US20100130591 ("the '591 Publication") (EX1024), Baker (EX1025), and Bennett (EX1026). (EX1011, 31–36.) According to the Office, a POSA would have arrived at the claimed target regions because "[w]hile the prior art has not specifically disclosed the recited sequences . . . , the prior art has clearly taught that such sequences are embraced within a known target region." (*Id.*) The Office stated: "the same region targeted by the instantly claimed oligomers is superior to other regions of exon 53" and the claimed target regions "fall squarely within" the target region that the '212 Publication taught to be "superior." (*Id.*) The Office explained:

"It would have been well within the skill of the artisan to test various sizes of oligomers in an optimization of antisense compounds targeting a known superior target region. It is noted that the superior target region is not large." (*Id.*) The Office quoted the statement in the '212 Publication that "[w]hen considering the data presented here as a whole, the superiority of the PMO targeting the sequence +30+59 (PMO-G, or h53A30/1), is strongly indicated." (*Id.*) The Office further stated that "[t]he modifications utilized in the invention and recited in the claims were well known and routinely used in the art at the time of invention," citing Baker and Bennett. (*Id.*)

In response, NS amended the claims to recite only AOs consisting of SEQ ID NOs: 11 and 57—the latter of which corresponds to an AO targeting the +36+60 sequence of exon 53—and argued that the claimed AOs "have superior skipping activity over exemplary oligomers taught in" the '212 Publication and the '591 Publication. (EX1011, 43–48.) Notably, NS did not dispute whether modifications recited in the rejected claims were well known and routine. (*Id.*)

The prior art rejection was maintained in a Final Office Action. The Office further explained that "[t]he fact that applicant screened for more oligonucleotides in a region that has been taught to be superior utilizing size ranges and modifications known in the art is not unexpected." (EX1011, 61.)

In response, NS further amended the claims to focus on a single AO sequence consisting of SEQ ID NO: 57 and argued that this AO consisting of the oligomer sequence of SEQ ID NO: 57 allegedly outperformed the "top performer" taught in '212 Publication, stating that "Popplewell [i.e., the '212 Publication] teaches that the oligomer corresponding to positions 30–59 of exon 53 [i.e., PMO-G] provides the highest activity." (EX1011, 64–71.) NS further alleged that "this superiority is unexpected, at least because none of the cited references teach or suggest such an effect." (*Id.*)

As described below, NS's unexpected results argument relied on an indirect and inappropriate comparison. In fact, NS's specification contained a *direct* comparison between an AO targeting the +36+60 sequence of exon 53 and another prior art AO that was the same length (25-mer) and complementary to positions 35 to 59 of exon 53 (+35+59)—just one position shifted from the claimed AO on exon 53. The data in NS's specification showed that an AO targeting the +36+60 sequence of exon 53 performed *no better* (and possibly worse) than an AO targeting the +35+59 sequence (the target sequence of PMO-A), contradicting NS's unexpected results arguments.

The Office issued a Notice of Allowance without further comment. (EX1011, 72–76.)

VI. State of the Art Before August 31, 2011

A. DMD

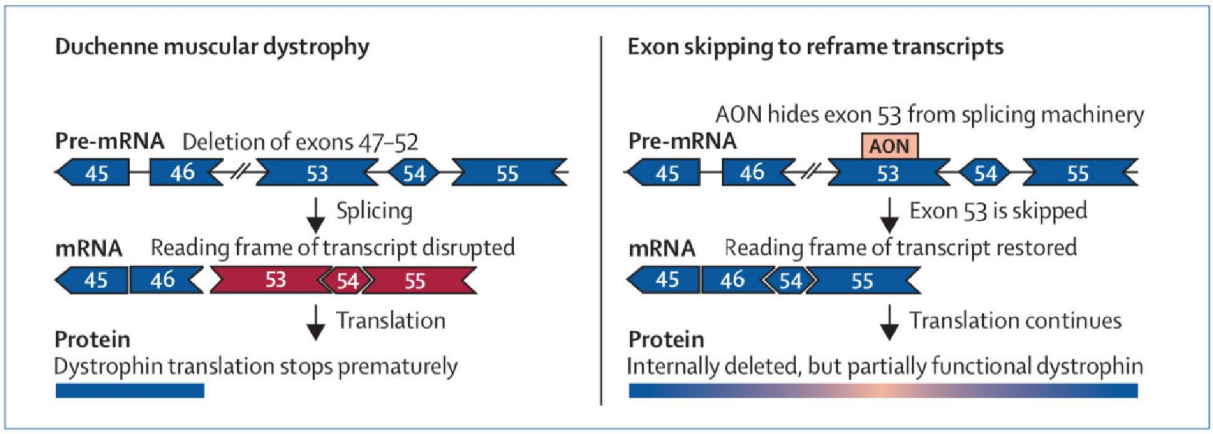
DMD is an X-linked, progressive neuromuscular disease which affects 1:3,500–6,000 newborn boys and causes progressive muscle weakness, cardiomyopathy, and respiratory failure. (EX1027, 77; EX1028, 918; EX1067, 644–645; EX1095, ¶¶21–29.) DMD patients lack functional dystrophin, a protein essential to the stability of muscle fibers. (*Id.*)

In DMD, dystrophin protein is not produced, typically because a frame-shift mutation disrupts the triplet reading frame, leading to premature termination of translation. (EX1028, 918–919; EX1029, 2721; EX1095, ¶30.) In contrast, in Becker muscular dystrophy (BMD), in-frame mutations in the dystrophin gene result in truncated but functional dystrophin. BMD patients experience milder symptoms than DMD patients, ranging from borderline DMD to no symptoms at all. (EX1028, 919; EX1030, 254; EX1031, 798; EX1067, 645; EX1095, ¶35.) Similarly, truncated but semi-functional dystrophin can be found in so-called "revertant fibers" in many DMD patients. (EX1031, 798–99; EX1095, ¶34.) Revertant fibers are believed to arise via alternative splicing of dystrophin pre-mRNAs. (*Id.*)

B. AOs in Exon Skipping Therapy in DMD

Exon skipping therapy in DMD has a natural precedent in the revertant fibers found in many DMD patients and in the truncated but functional dystrophin of BMD

patients. (EX1031, 798–799; EX1095, ¶36.) In exon skipping therapy, AOs target genetic mutations and bind to pre-mRNA so that the cellular machinery "skips over" one or more exons flanking the mutation, restoring the open reading frame. (EX1029, 2719–2720; EX1095, ¶¶32–33, 37.) Restoration of the reading frame results in production of truncated, semi-functional dystrophin protein (EX1031, 799; EX1032, 796; *see generally* EX1033; EX1095, ¶37), as illustrated in the figure below:



(Figure adapted from EX1043, 873, Fig. 1; EX1095, ¶37.) Levels of induced dystrophin transcript can be monitored with *in vitro* assays, for example through reverse transcriptase PCR (RT-PCR) and gel images using densitometric analysis. (EX1021, 103; EX1035, 1293, 1295; EX1095, ¶¶62–65.)

The dystrophin (or *DMD*) gene contains 79 exons. (EX1030, 255; EX1095, ¶31.) Based on epidemiological studies, exon 53 was widely identified in the literature as being a leading target exon for AO therapy with the potential to treat a

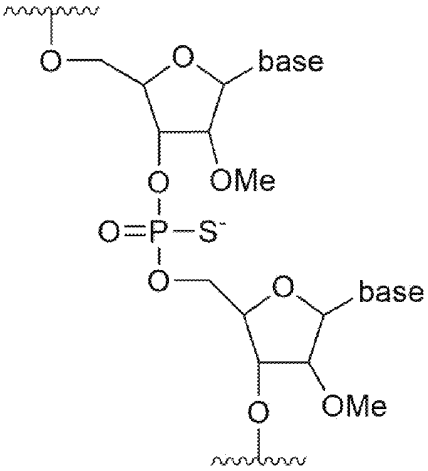
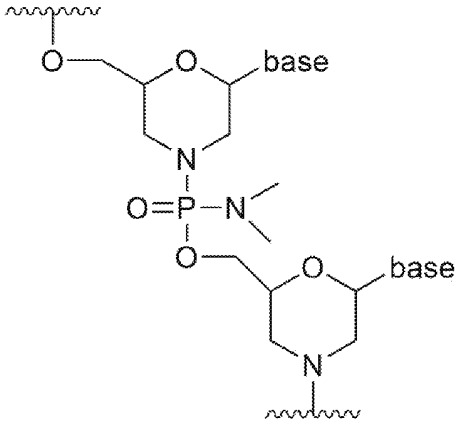
large number of DMD patients. (EX1021, 102–103; EX1036, 358, Table 1; EX1095, ¶¶31, 97.)

By August 31, 2011, exon skipping had been demonstrated in numerous *in vitro* and *in vivo* studies, including in DMD animal models. (EX1031, 800–801, Table 1 (listing *in vitro* and *in vivo* studies evaluating PMOs or 2'-OMePSs); EX1095, ¶38.) Further, two AOs targeting exon 51 were undergoing evaluation in clinical trials for the treatment of DMD: drisapersen (PRO051) and eteplirsen (AVI-4658). Early results from the clinical trials were encouraging, and both treatments were reported as of August 31, 2011, to induce exon skipping and increase dystrophin levels in DMD patients. (EX1037, 2684; EX1038, Abstract; EX1028, Abstract; EX1039, Abstract; EX1095, ¶39.)

As of August 31, 2011, AOs investigated for exon skipping therapy in DMD were typically short single-stranded oligomers, 20–30 bases in length. (EX1035, 1290, Table 1; EX1040, 495; EX1041, 32; EX1021, 109; EX1042, 548; EX1095, ¶37.) For example, the AOs being evaluated in DMD clinical trials were respectively 20 bases (PRO051) and 30 bases (AVI-4658) in length. (EX1043, 874, Table 1; EX1095, ¶¶44, 46.)

To improve the properties of AOs, scientists routinely used modified nucleobases, chemical backbones, and intersubunit linkages. (*See generally* EX1040; EX1044; EX1045; EX1095, ¶42.) These modified AOs were designed to

maintain their ability to bind to pre-mRNA through Watson-Crick base pairing. (EX1095, ¶42.) Two prominent classes of AOs as of August 31, 2011, were 2'-OMePSs and PMOs. Their structures are shown below:

Phosphorothioate-linked 2'-O-methyl ribose oligomer ("2'-OMePS")	**Phosphorodiamidate morpholino oligomer ("PMO")**
	

(Figure adapted from EX1040, 496, Fig. 1; *see also* EX1022, 155 ("The favorable safety profile of the uncharged PMOs has been remarkably consistent and predictable, as more than 460 patients have been safely dosed with PMO in clinical trials for a variety of indications."); EX1040, 495 ("[2'-OMePS] and PMO are the most frequently utilized because of their suitable properties"); EX1043, 873 ("The most commonly used chemistries for exon-skipping antisense oligonucleotides are 2'-O-methyl RNA with a negatively charged phosphorothioate backbone (2'-OMePS) and uncharged phosphorodiamidate morpholino oligomers (PMO) . . . ."); EX1095, ¶¶42–43.)

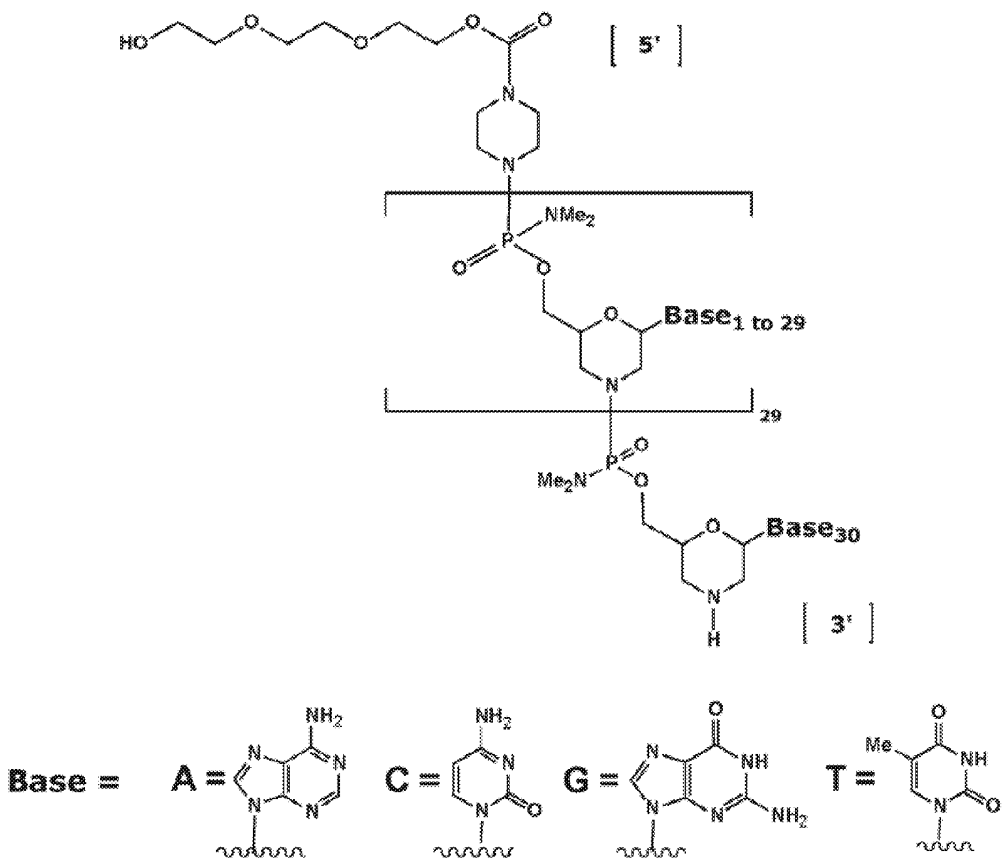
One of the two clinical candidates targeting exon 51 discussed above, PRO051, was a 2'-OMePS. (EX1095, ¶44.) 2'-OMePSs have a structure similar to RNA but the 2'-OH position of the ribose ring has been methylated, and instead of using a phosphodiester linkage between nucleotides, one of the non-bridging oxygen atoms of the phosphate group is substituted with a sulfur atom to create a phosphorothioate linkage. (EX1095, ¶44.)

AVI-4658, the other clinical candidate targeting exon 51 discussed above, was a PMO, a type of "morpholino." (EX1095, ¶46.) Morpholinos, including PMOs, contain a six-membered morpholinyl moiety instead of a ribose. PMO subunits are linked through uncharged phosphorodiamidate linkages. (EX1095, ¶46.)

By August 31, 2011, it was understood that the use of either 2'-OMePSs or PMOs did not typically influence exon skipping trends, indicating that optimization of AO design with AOs of one chemistry was considered applicable to AOs of the other chemistry. (EX1046, 2 ("The use of either 2OMeAOs or PMOs does not seem to influence exon skipping trends."); *id*., Abstract ("A hierarchy in exon skipping efficiency, observed with overlapping AOs composed of 2'-O-methyl modified bases, was also observed when these same sequences were evaluated as [PMOs], indicating design parameters established with one chemistry may be applied to the other."); EX1095, ¶48.)

As of August 31, 2011, PMOs were routinely modified at the 5' end by conjugation of chemical groups including amide moieties and triethylene glycol (or "TEG") moieties in order to improve the properties of the PMOs. (EX1053, 1307, Figure 1; EX1022, 145, Fig. 1; EX1095, ¶49.) Conjugation of a triethylene glycol moiety at the 5' end of a PMO, for example, was recognized as potentially improving solubility. (EX1047, ¶¶[0049], [0156]; EX1075, ¶[0044]; EX1076, ¶[0338]; EX1077, 12:9–11; EX1095, ¶50.) Methods for synthesizing PMOs with a TEG moiety conjugated at the 5' end were known in the art. (EX1075, ¶¶[0120]–[0123], [0131] (describing processes for introducing a TEG tail during PMO synthesis); EX1076, ¶¶[0664]–[0667], [0674] (same); EX1095, ¶139.)

As of August 31, 2011, it was known that Sarepta's (formerly AVI BioPharma Inc.) exon 51 skipping AO candidate, AVI-4658, was a PMO with the general structure illustrated below, including a triethylene glycol group attached at the 5' end:



(EX1022, 145, Fig. 1; EX1095, ¶¶50, 75.) As noted above, as of August 31, 2011, AVI-4658 was undergoing evaluation in clinical studies for the treatment of DMD. Early results from the clinical studies were encouraging and AVI-4658 was reported to induce exon skipping and to increase dystrophin levels in DMD patients. (EX1028, Abstract; EX1039, Abstract; EX1095, ¶39.) AVI-4658 was approved in 2016 by the FDA as the first disease-modifying treatment for DMD. (EX1095, ¶46.)

C. Prior Art AOs Targeting Exon 53 of Dystrophin

By August 31, 2011, large screens had identified AOs effective for exon skipping of virtually all exons of the dystrophin gene. (EX1095, ¶51.) Because it

represented a large patient population amenable to AO treatment, exon 53 was a focal point for research efforts, and multiple groups had developed AOs that could effectively induce skipping of this exon. (EX1095, ¶¶51–61.)

For example, in 2005, Aartsma-Rus and colleagues at Leiden University in the Netherlands reported on testing of 114 AOs targeting sequences within 35 exons of the dystrophin gene, most of which were found to induce exon skipping. (EX1048, Abstract; EX1095, ¶53.) The Leiden researchers identified h53AON1 (+45+62) as causing skipping of exon 53. (EX1048, 288; *see also* EX1049, 48, Table 2 (reporting that h53AON1 induces skipping of exon 53).)

In 2007, Wilton and colleagues reported on testing of 470 AOs designed to induce skipping of nearly every exon within the dystrophin pre-mRNA. (EX1035, 1289; EX1050, 34–63; EX1095, ¶54.) Wilton classified exons into four types based on how easily and effectively the exon could be skipped and excised from the mature mRNA. (EX1035, 1289; EX1095, ¶54.) Both exons 51 and 53 were classified as Type 1 exons, meaning that they could be skipped with high (greater than 30%) levels of exon-skipping efficiency. (EX1035, 1289–90; EX1095, ¶54.) Among the "most effective" AOs identified by Wilton was H53A(+39+69) targeting exon 53. (EX1035, 1290, 1293; EX1095, ¶54.) Similarly, a Wilton patent application published in 2006 disclosed H53A(+39+69) along with several additional effective

AOs targeting exon 53 and demonstrated that AOs targeting the +30+74 region of exon 53 induce exon skipping. (EX1050, 62–63, Table 39; EX1095, ¶54.)

A patent application published in 2007 filed by Matsuo and colleagues reported on testing of 93 AOs targeting a number of exons, including exon 53. (EX1051, ¶[1032]; EX1095, ¶55.) Matsuo reported that several AOs induced exon 53 skipping, including AO65 (+21+38), AO95 (+30+47), AO66 (+39+56), and AO67 (+57+74). (EX1051, ¶¶[0572], [0573], [1032]; EX1095, ¶55.)

In 2009, Popplewell and colleagues at Royal Holloway, University of London, reported on testing of 66 PMOs, 25 or 30 bases in length, designed to target exons 44, 45, 46, 51, and 53 of the dystrophin gene. (EX1052, 554; EX1095, ¶56.) For the exon 53-targeting-AOs, Popplewell and colleagues first designed an array of 17 PMOs, each 25 bases in length, to cover the whole of exon 53, with stepwise arrays over suggested bio-active sites. (EX1052, 555, Fig. 1 (showing design process for exon 53); EX1023, ¶¶[0085], [0096]; EX1095, ¶56.) These 25-mer PMOs were then tested in normal human skeletal muscle cells. (EX1023, ¶[0085]; EX1095, ¶56.) Based on the results of testing of the 25-mers, a 3-nucleotide stepped array of 30-mer PMOs was designed to target the region of exon 53 (+30+74), associated with exon skipping. (EX1052, 555, Fig. 1; EX1023, ¶[0086]; EX1095, ¶56.) The authors reported "[s]pecific, consistent and sustained exon skipping" for 44 of the 66 PMOs tested. (EX1052, 555.) The authors concluded: "We provide here direct evidence

that [AO] bioactivity shows a significant association with accessibility of its target site to binding." (*Id.*, 558.) Accessibility, in turn, was described as depending "directly on the secondary structure of the pre-mRNA." (*Id.*, 559.) The authors noted that the "[AOs] displaying the highest bioactivity in the work of Aartsma-Rus *et al.* and Wilton *et al.* show some degree of overlap with the hybridization peaks that we have defined for exons 45, 46, and 53." (*Id.*, 558–559.)

Preliminary results of Popplewell's testing of AOs targeted to exon 53 from the Popplewell 2009 study were provided in the '212 Publication (EX1023; published in July 2010) and the complete results of the study were reported in February 2010 in Popplewell. (EX1095, ¶57.) As described below, Popplewell reported the results of testing of 13 PMOs targeting different portions within the +29+74 sequence of exon 53 and found that *each and every one* of the AOs induced skipping. (EX1021, 106, Fig. 1b; EX1095, ¶57.)

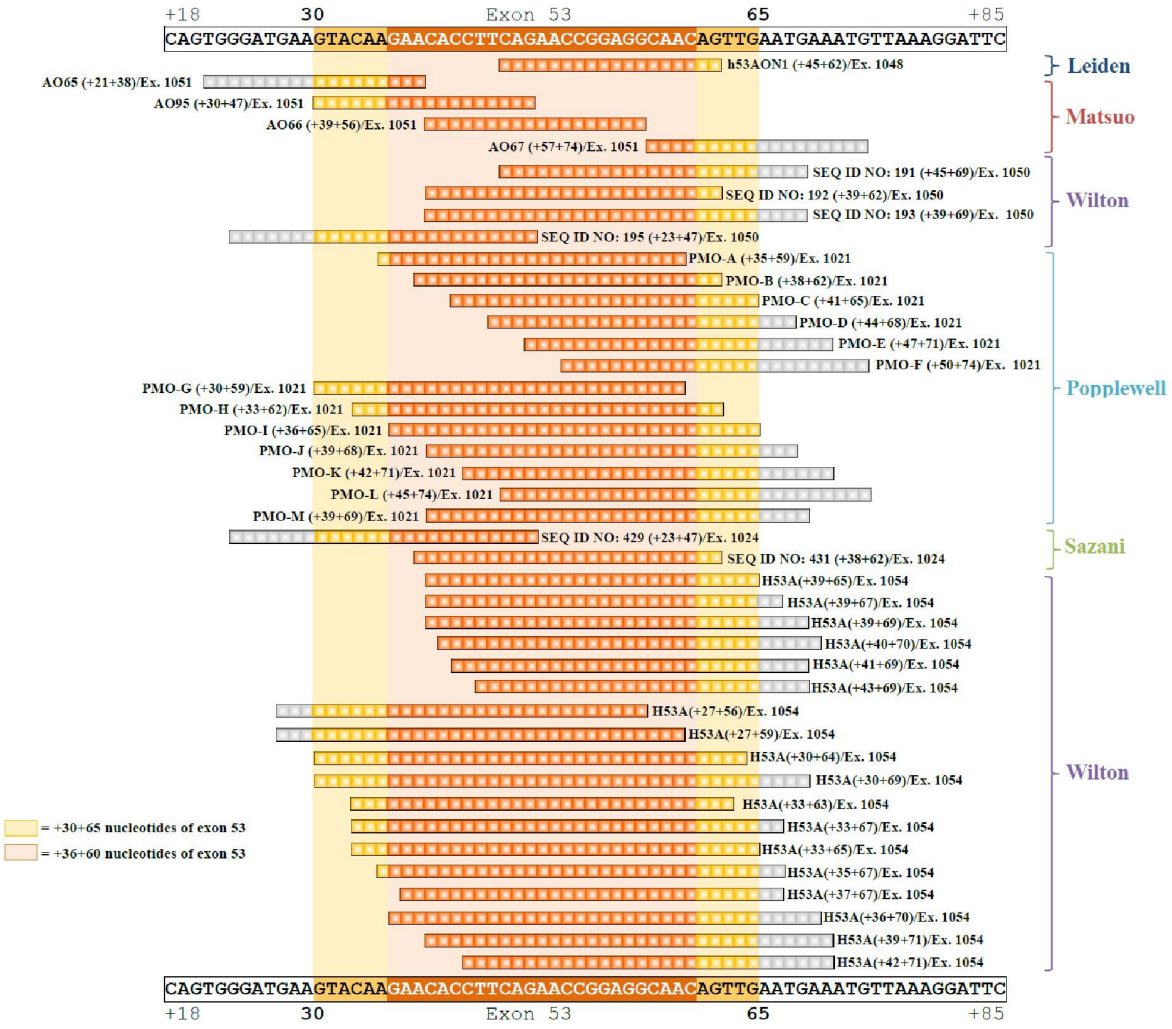
Popplewell and colleagues identified the 30th to 65th nucleotides of exon 53 (+30+65), in particular, as a hotspot target region resulting in effective AOs. (EX1021, 109; EX1095, ¶57.) Indeed, PMOs targeting this region were found to induce *in vitro* levels of exon skipping that were comparable to those reported pre-clinically for PRO051 and AVI-4658, the two AOs that were undergoing Phase I/II clinical trials for the treatment of DMD with encouraging results. (EX1021, 109; EX1095, ¶¶102, 110.)

In an April 2010 PCT publication, Sazani evaluated a series of overlapping AOs, each 25 bases in length, targeting exon 53. (EX1024, ¶[0293], Example 3.) The AOs were synthesized as peptide-conjugated PMOs (PPMOs), which are PMOs conjugated to cell-penetrating peptides. (EX1053, 1306; EX1095, ¶58.) Sazani identified three PPMOs that were most effective at inducing exon 53 skipping, including one targeting positions +38+62 of exon 53. (EX1024, ¶[0293], Example 3, Fig. 4G; EX1095, ¶58.)

In a patent application filed in November 2010,[3] Wilton evaluated a series of AOs targeting multiple exons including exon 53. (EX1054; EX1095, ¶59.) Wilton identified 18 AOs which overlapped with the +30 to +65 hotspot region, *all* of which induced skipping of exon 53. (EX1054, 58; EX1095, ¶59.)

The figure below summarizes select AOs that were evaluated as of August 31, 2011, and were reported to induce skipping of exon 53. Yellow highlighting denotes the 30th to 65th nucleotides of exon 53 identified by Popplewell as providing superior skipping and orange highlighting denotes the 36th to 60th nucleotides of exon 53.

[3] EX1054 was published in May 2011 in English as a PCT application designating the United States.



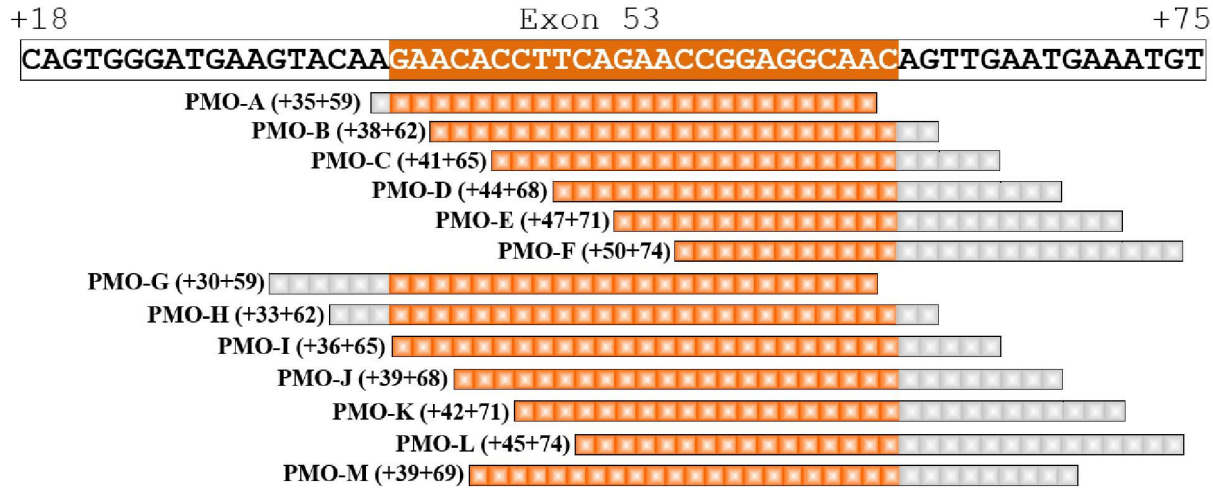
(EX1095, ¶61.)

D. The Asserted Prior Art

1. Popplewell

Popplewell is acknowledged as prior art in the "Background Art" section of the '092 patent and is cited on the face of the patent. (EX1001, 3:5–6.) Popplewell was not, however, raised by the Examiner or the applicants during prosecution of the '092 patent.

Popplewell discloses the results of testing in normal human skeletal muscle cells of 24 PMOs designed to target exon 53 of the dystrophin gene. (EX1021, 104–105, Table 1; EX1095, ¶67.) Popplewell discloses additional testing of 13 of the PMOs "whose target sites are within the sequence +29 to +74 of exon 53, the region previously shown to be in open conformation, binding to which interferes with spliceosome-mediated pre-mRNA splicing, such that exon 53 is skipped." (EX1021, 104; EX1095, ¶67.) The sequences of these 13 PMOs are shown in the figure below, along with the +36+60 sequence of exon 53 (recited in the claims of the '092 patent), which is highlighted in dark orange. Light orange highlighting denotes the bases targeting the +36+60 sequence of exon 53.



(EX1095, ¶67.) Notably, PMO-A targets the +35+59 sequence. PMO-A is therefore the same length as an AO consisting of a "25-mer oligomer" claimed in the '092 patent (i.e., both AOs are 25-mers). PMO-A also targets a sequence within exon 53

shifted just one nucleotide towards the 5' end of exon 53 as compared to the claimed AO of the '092 patent (i.e., PMO-A targets the +35+59 sequence whereas the claimed AO of the '092 patent targets the +36+60 sequence). (EX1095, ¶68.)

The 13 PMOs targeting the +29+74 sequence were compared directly in DMD patient cells at a 300 nM dose administered by nucleofection. (EX1021, 104; EX1095, ¶69.) Each of the 13 PMOs tested gave exon skipping levels of at least 15%. (*Id.*) Moreover, based on the results of the testing, Popplewell characterizes the following PMOs as "Type 1" PMOs (i.e., "most effective," with levels of exon skipping over 50%): PMOs -A, -B, -G, -H, -I, and -M. (EX1021, 104; EX1095, ¶69.) In addition to testing in DMD patient cells, Popplewell includes both Western blot analyses of DMD patient cell lysates and testing in a humanized mouse model. (EX1021, 105–107; EX1095, ¶¶71–72.) Skipping of exon 53 was observed for each of the PMOs tested. (*Id.*) In the *in vivo* humanized mouse model, PMO-A showed the highest skipping efficiency (8%), followed by PMO-I (7.6%), PMO-G (7.2%), and PMO-H (4.8%). (*Id.*, 107; EX1095, ¶72.)

In discussing the results, the Popplewell authors conclude: "When considering the data presented previously and here as a whole, the superiority of the PMOs targeting the sequence +30+65 (i.e., PMOs -A, -B, -G and -H) is strongly indicated." (EX1021, 109; EX1095, ¶73.) While Popplewell recommends PMO-G as "the PMO of choice for the targeted skipping of exon 53 . . . based primarily on its more

persistent longevity of action," the authors state that PMO-A targeting (+35+59) and PMO-H targeting (+33+62) are "viable alternatives." (EX1021, 109; EX1095, ¶73.)

2. Sazani

Sazani reports on the results of late-stage pre-clinical safety and genotoxicity evaluations of AVI-4658, Sarepta's exon 51-targeted exon skipping therapy, which was approved by FDA in 2016. Figure 1 of Sazani, reproduced above (*supra* § VI.B), depicts the general structure of AVI-4658, a PMO with a triethylene glycol moiety at its 5'-end. (EX1022, 145, Fig. 1; EX1095, ¶75.)

The triethylene glycol moiety at the 5' end of AVI-4658 shown in Figure 1 of Sazani is the same moiety recited in claim 3 of the '092 patent. (EX1095, ¶76.) Likewise, each phosphorodiamidate morpholino monomer of AVI-4658 shown in Figure 1 of Sazani is the same monomer recited in claims 2 and 3 of the '092 patent. Sazani concludes that the favorable safety profile of AVI-4658 is consistent with numerous other clinical trials where PMOs showed no toxicity and allowed the initiation of clinical trials in DMD patients. (EX1022, Abstract, 155; EX1095, ¶77.)

VII. Level of Ordinary Skill in the Art

Petitioner submits, solely for purposes of this IPR, that a POSA for the claimed subject matter of the '092 patent would have a Ph.D. in chemistry, biochemistry, cell biology, genetics, molecular biology, or an equivalent, and several years of experience with AOs for inducing exon skipping. A POSA would also have

familiarity with methods for making and testing the safety and efficacy of such AOs, both *in vitro* and *in vivo*, and the use of AOs for inducing exon skipping in the context of medical conditions, such as DMD, that may be treated by administering such AOs. (EX1095, ¶92.) Further, a POSA would have knowledge of and experience with chemical modifications that may be incorporated into AOs, such as modifications to the backbone and/or nucleobases of the AOs, and the potential impact of those modifications on the utility of the AOs. (EX1095, ¶93.)

VIII. Detailed Explanation of Ground

A. Ground 1: Claims 1–3 Are Obvious Over Popplewell and Sazani

Popplewell and Sazani disclose or suggest all elements of claims 1–3 of the '092 patent. (*Supra* § VI.D; EX1095, ¶¶66–77.) A POSA would have had reason to combine the teachings of Popplewell and Sazani in order to achieve the claimed AOs and would have had a reasonable expectation of success in arriving at the claimed subject matter.

1. A POSA Would Have Been Motivated to Generate a PMO of Claim 1

a) The Prior Art Recommended AOs Targeting Exon 53 as a Promising Treatment for DMD

Prior to August 31, 2011, researchers had recognized the promise of AO-induced exon skipping therapy for treating DMD and had identified exon 53, in

particular, as a target of such AOs given its potential to treat large numbers of patients. (EX1021, 102–103; EX1036, 358, Table 1; EX1095, ¶¶96–97.)

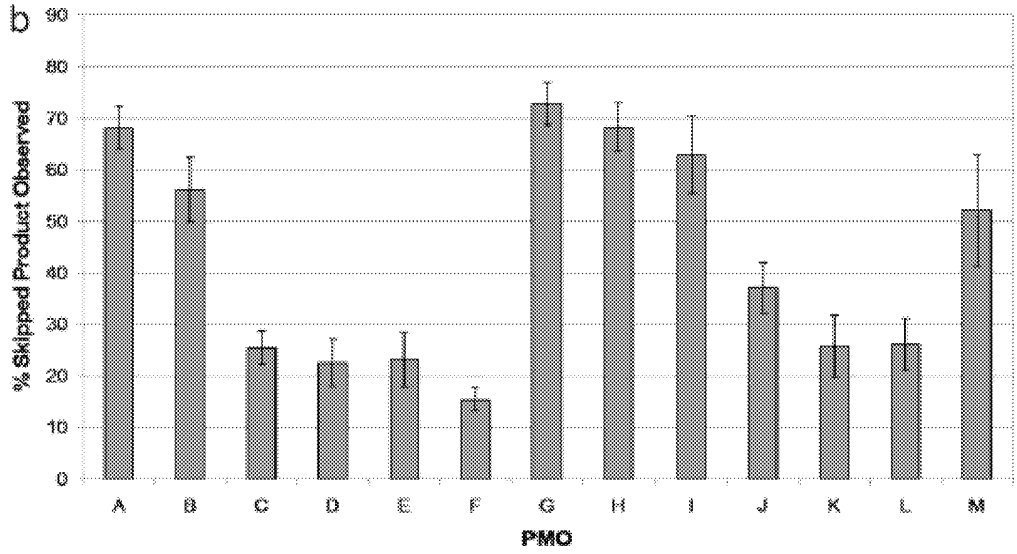
As recognized by Popplewell, this "exciting" therapy, targeted to exon 53 of dystrophin, had the potential to treat a reported approximately 8–13.5% of DMD patients. (EX1021, 102–103; EX1036, 358, Table 1; EX1095, ¶97.) Along with AOs targeting exon 51 and exon 45, AOs targeting exon 53 were reported to have the potential to treat a large number of DMD patients. (*Id.*) In fact, it was reported in 2008 that AVI BioPharma Inc. (renamed as Sarepta) and members of the MDEX consortium (a multidisciplinary enterprise created to promote translational research into muscular dystrophies) were considering exon 53 as the next target exon. (EX1056, 273; EX1095, ¶98.) Similarly, in June 2010, GlaxoSmithKline and Prosensa Holding N.V. ("Prosensa") (a predecessor company to BioMarin Pharmaceutical Inc.) announced a research program focused on skipping of exon 53. (EX1059; EX1095, ¶98.) Thus, the prior art provided express motivation to generate exon 53 skipping AOs. (EX1095, ¶¶96–98.)

Proof-of-principle in humans had been demonstrated in two ongoing clinical trials evaluating exon 51-targeting AOs. (EX1037, 2684; EX1038, Abstract; EX1028, Abstract; EX1039, Abstract; EX1056, 269; EX1095, ¶96.) AO-induced exon skipping therapy was widely recognized as a promising DMD treatment worthy of further investigation with respect to additional target exons other than exon 51.

(*See, e.g.*, EX1048, Abstract ("As small molecule drugs for [DMD], [AOs] have been shown to restore the disrupted reading frame of DMD transcripts by inducing specific exon skipping. This allows the synthesis of largely functional dystrophin proteins and potential conversion of severe DMD into milder [BMD] phenotypes."); EX1035, 1294 ("With increasing experience of AOs and AO chemistries, we anticipate that the risk:benefit profile of these compounds could facilitate a rapid introduction into the clinic to address the many different dystrophin mutations that lead to DMD."); EX1057, Abstract ("[E]xon skipping is currently one of the most promising therapeutic tools for DMD, and a successful first-in-man trial has recently been completed."); EX1052, 554 ("Exon skipping induced by [AOs], generally based on an RNA backbone, is a future hope as a therapy for DMD. Indeed, by skipping out-of-frame mutations of the *DMD* gene, the reading frame can be restored and a truncated, yet functional, [BMD]-like dystrophin protein is expressed."); EX1058, Abstract ("Proof-of-concept of exon skipping has been obtained in animal models, and most recently in clinical trials; this approach represents a promising therapy for a subset of patients."); EX1041, 34 ("Exon skipping using AO drugs has rapidly emerged as the frontline therapeutic approach for DMD.").)

b) The Prior Art Identified an Effective Target Region of Exon 53 that Encompasses the Target Sequence of the Claimed AOs

As Popplewell recognized, prior AO studies had identified the 29th to 74th nucleotides within exon 53 of dystrophin mRNA as a target region for skipping of exon 53. (EX1021, 104; EX1095, ¶¶51–61.) Indeed, each and every one of the 13 PMOs Popplewell tested targeting the +29+74 region induced skipping of exon 53 in DMD patient cells, as shown in Figure 1b of Popplewell, reproduced below:



(EX1021, 106, Fig. 1b; EX1095, ¶¶69, 100.)

Within this larger (+29+74) active region of exon 53, Popplewell found that, in particular, the 30th to 65th nucleotides of exon 53 define a hotspot target region for effective AOs. (*See e.g.* EX1021, 108 ("The data presented here would indicate that PMOs targeting within the sequence +30+65 of exon 53 (namely PMO-A, -G, and -H) produce levels of exon skipping that may be considered effective (over 50%

exon skipping)."), 109 ("When considering the data presented previously and here as a whole, the superiority of the PMOs targeting the sequence +30+65 (i.e. PMOs -A, -B, -G and -H) is strongly indicated.").) Indeed, Popplewell highlighted that the levels of skipping produced *in vitro* by PMOs targeting the sequence +30+65 were comparable to those reported pre-clinically for PRO051 and AVI-4658. (EX1021, 109.) Popplewell concluded: "We would therefore recommend that PMOs targeting sequence +30+65 of exon 53 of the *DMD* gene worthy of consideration for any upcoming clinical trial." (EX1021, 109.)

Popplewell categorized the top performing PMOs as "Type 1" PMOs. These included 25-mer and 30-mer PMOs, as well as a prior art 31-mer PMO. (EX1021, 109 ("In this study, sequence +30+65 was effectively targeted by PMOs -A, -B, -G, and -H, resulting in exon 53 skipping."), 104 ("PMOs -G, -H, and -A were the most efficient, producing a mean of 73% (±4.10%), 68% (±4.77%) and 68% (±4.14%) exon skipping respectively (classified as Type 1) (Fig. 1). The other PMOs tested produced the following skipping levels: PMO-I, 63% (±7.5%); PMO-B, 56% (±6.29%); PMO-M, 52% (±10.78%) (all classified as Type 1); PMO-J, 37% (±4.95%); (classified as Type 2). All other PMOs tested gave exon skipping at levels of between 15% and 26%."); EX1095, ¶101.)

In view of the successful results of Popplewell, a POSA would have been motivated to generate a 25-mer PMO targeting a sequence within the 30th to 65th

hotspot region of exon 53. (EX1095, ¶106.) The (+36+60) target sequence for the PMOs of claim 1 of the '092 patent falls squarely within the hotspot target region taught by Popplewell. (EX1095, ¶16.)

c) A POSA Would Have Been Motivated to Generate a PMO Targeting the 36th to 60th Nucleotides of Exon 53

Two of the PMOs reported in Popplewell as Type 1 PMOs that effectively target the +30+65 sequence of exon 53 were 25-mers: PMOs -A and -B. (EX1021, 109.) Of these two, the authors of Popplewell considered PMO-A, which targets (+35+59), to be more effective at inducing exon 53 skipping. (*See, e.g.*, EX1021, 109 (PMO-A provides a "viable alternative" for targeted skipping of exon 53); EX1095, ¶108.)

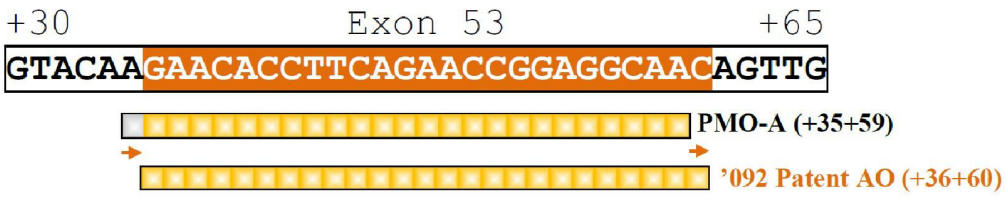
A POSA would have been motivated to further optimize the target sequence of the most effective 25-mer, PMO-A (+35+59), by using the same routine AO screening techniques employed by Popplewell (and others) to identify additional effective AOs. (EX1095, ¶111.) *See In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (the "[t]he normal desire of scientists or artisans to improve upon what is already generally known provides the motivation" to discover optimal conditions within a known range). In particular, a POSA would have generated PMOs in a one-nucleotide stepped array, using the AOs identified in Popplewell as most promising, including an AO targeting (+35+59), as starting sequences, and would have tested

these AOs for their ability to induce exon 53 skipping. (EX1095, ¶112.) Indeed, Popplewell recognizes that a "stepped base-by-base screening of AOs across the entirety of exon 53 . . . might reveal an AO with a better dose-response and longevity of action profile." (EX1021, 108.)

A stepwise array AO screening technique, such as the technique used by Popplewell, was routinely used by researchers in the field to optimize AO sequences once initial effective sequences had been identified. (EX1024, ¶[0293], Example 3 (designing an array of 24 AOs each 25 bases in length, targeting exon 53); EX1060, 1340 ("Identification of potent antisense sequences has often been based upon empirical approaches to oligonucleotide selection because the optimal target site on the mRNA cannot yet be predicted. Many investigators employ oligonucleotide 'walks', spacing oligonucleotides of a given length at intervals along the RNA and choosing the one with the most activity."); EX1050, 36 ("Once efficient exon skipping had been induced with one antisense molecule, subsequent overlapping antisense molecules may be synthesized and then evaluated in the assay as described above."); EX1095, ¶111.)

Using the AO screening approach discussed above, a POSA, starting from the AOs identified in Popplewell as most promising, including PMO-A, would have quickly landed on a PMO with a sequence that is 100% complementary to the +36+60 sequence of exon 53 as claimed in claim 1 of the '092 patent. (EX1095,

¶112.) A POSA would have readily appreciated that such a PMO would hybridize to the corresponding human dystrophin pre-mRNA via Watson-Crick base pairing under physiological conditions as recited in claim 1 of the '092 patent. (EX1095, ¶112.) As shown in the figure below, the PMOs claimed by the '092 patent are the same length as PMO-A (both AOs are 25-mers) and target a sequence within exon 53 that is shifted just *one nucleotide* towards the 3' end of exon 53 as compared to PMO-A (i.e., the PMOs of the '092 patent target the +36+60 sequence whereas PMO-A targets the +35+59 sequence).



(EX1095, ¶112.)

A POSA would have been motivated to generate and test an AO with a PMO backbone in view of the exon 53 skipping efficacy of the PMOs reported on in Popplewell. (EX1095, ¶115.) A POSA would have understood that PMOs may contain either thymine or uracil bases, and that either base would be complementary to an adenine base found in pre-mRNA and would pair with adenine via Watson-

Crick base pairing under physiological conditions.[4] (EX1023, ¶[0028] (describing PMOs containing T's); EX1055, Fig. 1 (showing PMO modification and indicating bases are selected from A, C, G, T, and U), Fig. 5 (evaluating a morpholino oligomer having a sequence with U's); EX1095, ¶117.) A PMO consisting of a 25-mer oligomer that is 100% complementary to the +36+60 sequence of exon 53 (and which would thus hybridize to the corresponding sequence in human dystrophin pre-mRNA with Watson-Crick base pairing under physiological conditions) meets all of the limitations of claim 1 of the '092 patent. (EX1095, ¶118.)

To the extent NS argues that Popplewell points to 30-mers as opposed to 25-mers as preferred embodiments, it is well settled that preferred embodiments do not constitute a teaching away from somewhat less preferred embodiments. *In re Susi*, 440 F.2d 442, 446, n.3 (C.C.P.A. 1971); *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir.

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[4] By obtaining claims to PMOs with thymines even though the only exemplified AO targeting the +36+60 sequence is a 2'-O-MePS containing uracils instead of thymines, NS tacitly acknowledged that the substitution of uracils for thymines in a PMO sequence would have been obvious. (*See* EX1001, claims 2 & 3 (directed to a PMO consisting of a 25-mer AO that is 100% complementary to the 36th to 60th nucleotides in exon 53 wherein each base is selected from the group consisting of cytosine, *thymine*, adenine, and guanine); *see* EX1095, ¶¶45, 47.)

1994) ("A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use."); *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) ("[I]n a section 103 inquiry, the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.") (quotation omitted)). Regardless, far from criticizing 25-mers, Popplewell concludes that the 25-mer PMO-A should be considered a "viable alternative" to the 30-mer PMO-G as a clinical candidate. (EX1021, 109; EX1095, ¶119.) Indeed, the 25-mer PMO-A performed better than several of the 30-mer AOs tested in Popplewell and had the highest *in vivo* efficacy of *any* PMO tested by Popplewell in the humanized DMD mouse. (*Id.*) Notably, the European Opposition Division recently found that similar claims were not inventive over Popplewell's PMO-A, "one of the preferred oligomers." (EX1086, 4–6.)

Additional considerations would also have motivated a POSA to use 25-mers, including limiting off-target effects, relative ease of synthesis, and reduced manufacturing costs associated with shorter AOs. (EX1095, ¶120.) As a general matter, as AO length increases, so do synthesis challenges and manufacturing costs. (EX1095, ¶120.) For this reason, scientists often favored the shorter of two AOs where similar efficacy was observed, and indeed one of the two AOs in human DMD clinical trials was only 20 bases in length. (*Id.*, ¶¶40–41, 44; EX1043, 874, Table 1.)

In an unrelated case, the Office previously found that the '212 Publication and Popplewell do not teach away from a 25-mer. (EX1062, 15–17.) During prosecution of U.S. Application No. 14/776,533, where Petitioner filed claims to a 25-mer AO targeting the (+36+60) sequence in exon 53 with a TEG moiety at the 5' end, the Examiner rejected the pending claims over the Popplewell '212 Publication and explained that it does not criticize or discourage making a 25-mer PMO. (*Id.*) While Sarepta argued during prosecution of that case that a POSA would have selected PMO-G as the lead compound based on the teachings of the '212 Publication, Sarepta has since acquiesced to the Office's position and abandoned the case and arguments made therein. (EX1063, 1–2.)

Thus, a POSA would have been motivated to optimize the target sequence of PMO-A and using routine techniques would have quickly identified a PMO that is 25 bases in length and is 100% complementary to the +36+60 sequence of exon 53 (and which would thus hybridize to the corresponding sequence in human dystrophin pre-mRNA with Watson-Crick base pairing under physiological conditions) as claimed in claim 1 of the '092 patent.

2. A POSA Would Have Had a Reasonable Expectation of Successfully Making a PMO of Claim 1 that Induces Exon 53 Skipping

A POSA would have had a reasonable expectation of success in making a 25-mer PMO that is 100% complementary to the +36+60 sequence of exon 53 (and would thus hybridize to the corresponding human dystrophin pre-mRNA with Watson-Crick base pairing under physiological conditions) and that induces exon 53 skipping. (EX1095, ¶¶124–130.) "Obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). In this case, Popplewell demonstrates that multiple PMOs complementary to the +30+65 hotspot of exon 53 could be successfully made and evaluated for their ability to induce exon 53 skipping. (EX1095, ¶125.) Every PMO targeting the +30+65 hotspot of exon 53 tested in Popplewell (i.e., PMOs -A, -B, -C, -G, -H, and -I) induced skipping of exon 53. (EX1021, 106, Fig. 1b; EX1095, ¶125.)

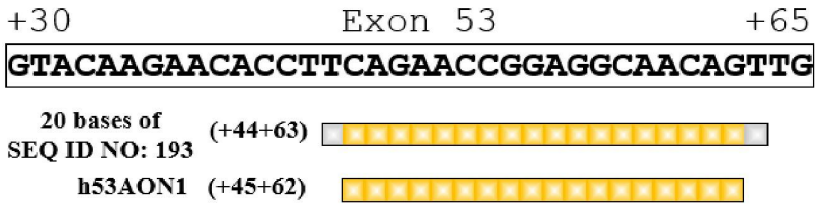
Methods for generating the PMOs were straightforward: as NS acknowledges in the specification, PMOs could be produced in accordance with methods known in the art or even ordered from a company. (EX1001, 13:15–19, 14:16–19, 14:47–49, 31:11–12; EX1035, 1294–1295; EX1065, 584; EX1049, 26; EX1050, 35; EX1054, 33; EX1024, ¶[0097]; EX1095, ¶¶121–122.) In Popplewell, the PMOs were ordered from the company Gene Tools LLC. (EX1021, 103; EX1095, ¶121.) Known methods for evaluating the ability of a PMO to induce exon 53 skipping are described in the "Materials and methods" section of Popplewell. (EX1021, 103; EX1095, ¶123.)

Further, as Dr. Corey explains, given the large number of overlapping PMOs tested in Popplewell targeting the +30+65 hotspot of exon 53, all of which were found to successfully induce exon 53 skipping, a POSA would have reasonably expected that a PMO targeting the +36+60 sequence would induce exon 53 skipping. (EX1095, ¶128.)

Not only does a 25-mer PMO that is 100% complementary to the +36+60 sequence of exon 53 as claimed in the '092 patent have a target sequence that is shifted only one base towards the 3' end of exon 53 as compared to the target sequence of PMO-A (+35+59), but Popplewell identified additional effective PMOs with target sequences that fully encompassed the +36+60 sequence. (EX1095, ¶127.) For example, PMO-H targeted the +33+62 sequence and PMO-I targeted the +36+65

sequence. (EX1021, 105, Table 1; EX1095, ¶127.) The ability of all of these AOs to induce skipping as reported in Popplewell confirms that a POSA would have had a reasonable expectation that an AO targeting the +36+60 sequence would induce skipping of exon 53. (EX1095, ¶¶126–127.)

In *University of Western Australia v. Academisch Ziekenhuis Leiden*, the Board considered claims with a filing date of September 2005 that were directed to AOs that induce exon 53 skipping. (EX1064 (Interference No. 106,007, Paper No. 476, May 12, 2016).) The Board found that as of 2005 "those working in the art were . . . aware that a degree of exon skipping capability would likely be maintained due to a change in a small number of complementary nucleobases of an [AO] known to cause skipping." (*Id.* at 41.) For example, the Board held that the prior art 18-mer h53AON1, targeting the +45+62 sequence of exon 53 (EX1049, 48, Table 2), rendered obvious claims in a patent directed to AOs with at least 20 consecutive bases of SEQ ID NO: 193, targeting the +39+69 sequence of exon 53. (EX1064, 38–42.) The Board explained: "It would have been obvious, for example, to add the two complementary nucleobases dictated by the known sequence of exon 53 to either end of h53AON1 with a reasonable expectation that the resultant 20 base [AO] would cause exon skipping." (*Id.* at 42.) The prior art h53AON1 as compared to the claimed AO with at least 20 consecutive bases of SEQ ID NO: 193 considered by the Board is illustrated below:



The Board's finding regarding the predictability of exon skipping in 2005 further supports that by August 31, 2011 a POSA would have had a reasonable expectation that a PMO that is 100% complementary to the +36+60 sequence of exon 53 and with a target sequence that is shifted just *one nucleotide* as compared to the target sequence of an effective prior art AO would also induce exon skipping.

3. A PMO of Claim 1 Would Have Been Obvious

As described above, the subject matter of claim 1 of the '092 patent would have been obvious to a POSA. (EX1095, ¶¶95–130.) By August 31, 2011, the prior art had identified exon 53 as a promising target for AO-induced exon skipping therapy. Popplewell had further identified the +30+65 region of exon 53 as a superior target region for AOs causing exon 53 skipping, and expressly identified PMO-A (+35+59) as a viable clinical candidate. Sazani had described the chemical structure of clinical candidate AVI-4658 as a PMO with a triethyl glycol moiety at its 5'-end and provides important safety information regarding AVI-4658. (EX1022, 145, Fig. 1; EX1095, ¶75.) A POSA would have been motivated to generate a PMO 100% complementary to the +36+60 sequence of exon 53 (which would thus hybridize to

the corresponding sequence in human dystrophin pre-mRNA with Watson-Crick base pairing under physiological conditions) as part of a routine AO stepwise array screening in order to optimize the PMOs tested in Popplewell, including PMO-A. In view of the overlapping PMOs targeting the +30+65 sequence of exon 53 that were reported to induce exon skipping, a POSA would have reasonably expected that a PMO targeting the +36+60 sequence of exon 53 would induce skipping of exon 53. Thus, the subject matter of claim 1 as a whole would have been obvious, as it encompasses nothing more than the application of routine prior art techniques for optimizing prior art AO sequences for exon skipping.

4. Claims 2 and 3 Are Obvious Over Popplewell and Sazani

Claims 2 and 3, the remaining claims of the '092 patent, recite additional limitations that were already described in the prior art. (EX1095, ¶¶131–141; *supra* § VI.)

a) Claim 2

As discussed above, claim 2 is identical to claim 1, except it additionally specifies the structure of the PMO monomer (N,N-dimethyl phosphorodiamidate) and recites that the "Base" of each monomer is cytosine, thymine, adenine, or guanine. A POSA would have had reason to combine the teachings of Popplewell and Sazani in order to achieve a PMO of claim 2 and would have had a reasonable expectation of success in arriving at the claimed subject matter.

A POSA would have been motivated, with a reasonable expectation of success, to make and use a PMO 100% complementary to the +36+60 sequence of exon 53 (which would thus hybridize to the corresponding sequence in human dystrophin pre-mRNA with Watson-Crick base pairing under physiological conditions) using the claimed PMO monomer subunit of the '092 patent. (EX1095, ¶¶132–135.) The PMO monomer subunit recited in claim 2 of the '092 patent was routinely used in constructing PMOs as of August 31, 2011. (EX1044, 536, Fig. 2; EX1040, 496, Fig. 1; EX1095, ¶133.) For example, as disclosed in Sazani, the same PMO monomer subunit containing cytosine, thymine, adenine, or guanine was present in AVI-4658, one of the two exon 51-targeting AO candidates undergoing clinical studies as of August 31, 2011. (EX1022, 145, Fig. 1; EX1095, ¶133.) A POSA would have been motivated, with a reasonable expectation of success, to make and use a PMO 100% complementary to the +36+60 sequence of exon 53 (which would thus hybridize to the corresponding sequence in human dystrophin pre-mRNA with Watson-Crick base pairing under physiological conditions), with the PMO monomer with the formula disclosed in Sazani, wherein each nucleobase is selected from cytosine, thymine, adenine, and guanine. (EX1022, 145, Fig. 1; EX1095, ¶135.)

For these reasons and those set forth above for claim 1, a POSA would have had motivation and a reasonable expectation of success in making an effective PMO

that is 100% complementary to the +36+60 sequence of exon 53 (which would thus hybridize to the corresponding sequence in human dystrophin pre-mRNA with Watson-Crick base pairing under physiological conditions), that contains the recited PMO monomeric subunit, wherein each nucleobase is selected from cytosine, thymine, adenine, and guanine as recited in claim 2 of the '092 patent. (EX1095, ¶135.)

b) Claim 3

As discussed above, claim 3 is identical to claim 2, except it additionally recites that the 25-mer PMO is attached to a triethylene glycol moiety at its 5' end. A POSA would have had reason to combine the teachings of Popplewell and Sazani in order to achieve a PMO of claim 3 and would have had a reasonable expectation of success in arriving at the claimed subject matter.

A POSA would have been motivated to modify a PMO targeting the +36+60 sequence by adding at the 5' end the triethylene glycol modification taught by Sazani. (EX1095, ¶138.) Conjugation of a triethylene glycol moiety to the 5' end of a PMO was a routine modification recognized in the art as potentially improving solubility. (EX1047, ¶¶[0049], [0156]; EX1075, ¶[0044]; EX1076, ¶[0338]; EX1077, 12:9–11; EX1095, ¶50.) The same 5' triethylene glycol moiety claimed in claim 3 of the '092 patent was present in AVI-4658, one of the two exon 51-targeting

AO candidates undergoing clinical studies as of August 31, 2011. (EX1022, 145, Fig. 1; EX1095, ¶140.)

For these reasons and those set forth above for claims 1 and 2, a POSA would have had motivation and a reasonable expectation of success in making an effective PMO that is 100% complementary to the +36+60 sequence of exon 53 (which would thus hybridize to the corresponding sequence in human dystrophin pre-mRNA with Watson-Crick base pairing under physiological conditions), that contains the recited PMO monomeric subunit, wherein each nucleobase is selected from cytosine, thymine, adenine, and guanine, and has a triethylene glycol moiety attached at the 5' end. (EX1095, ¶141.)

B. Secondary Considerations Do Not Support Nonobviousness

1. There Is No Evidence of Unexpected Results as NS Incorrectly Argued During Prosecution

During prosecution of the grandparent application, NS argued that a 2'-OMePS targeting the +36+60 sequence of exon 53, referred to as H53_36-60, had unexpected superiority over the "top performer" disclosed in the '212 Publication (PMO-G, (+30+59)). (EX1011, 69–71.) To make this argument, NS had to stitch together unrelated data from several separate studies. (*Id.*)

In particular, NS argued that Figures 2–4 of the specification showed that PMO No. 3 (having the sequence of SEQ ID NO: 11 (+32+56)) outperformed PMO

Nos. 12 and 15 (having the same target sequence as the "top performer" PMO-G (+30+59) in the '212 Publication and Popplewell). (*Id.*) NS next argued that Figures 16–17 of the specification showed that a 2'-OMePS having the sequence of SEQ ID NO: 57 (+36+60) outperformed a 2'-OMePS complementary to the same target sequence as SEQ ID NO: 11 (+32+56). (*Id.*) Applying the transitive property, NS argued that an AO of SEQ ID NO: 57 targeting (+36+60) would therefore display superior skipping activity over a 30-mer AO with the same target sequence as PMO-G (+30+59). (*Id.*; EX1095, ¶¶142–146.) The table below summarizes the characteristics of the AOs from Figures 2–4 and 16–17 that NS pointed to in arguing the alleged superiority of an AO of SEQ ID NO: 57 over PMO-G in the '212 Publication.

AO Name	Target Region	Length	5'-End	Backbone	Figure
PMO No. 3 (SEQ ID NO: 11)	+32+56	25	hydroxyl	PMO	2, 3, 4
PMO No. 12 (SEQ ID NO: 39)	+30+59 (PMO-G target sequence)	30	amide	PMO	2, 3
PMO No. 15 (SEQ ID NO: 39)	+30+59 (PMO-G target sequence)	30	hydroxyl	PMO	4
H53_32-56 (SEQ ID NO: 101)	+32+56	25	N/A	2'-OMePS	16, 17
H53_36-60 (SEQ ID NO: 57)	+36+60	25	N/A	2'-OMePS	16, 17

(EX1095, ¶¶142–143.)

NS's indirect comparison cannot be relied on. As explained by Dr. Corey, the various experiments differed in significant aspects, including AO backbone chemistry, AO length, AO 5'-end modification, cell type, and transfection reagents—all of which affect skipping efficiency. (EX1095, ¶145.) Further, NS failed to evaluate multiple AO concentrations and their studies lacked error bars. These limitations undermine NS's allegations of purported superiority. (*Id.*)

In contrast, a *direct* comparison contained in NS's specification, overlooked by the Examiner, shows that AOs targeting the same sequence as PMO-A (+35+59) from Popplewell worked as well as (or perhaps better than) AOs targeting the +36+60 sequence of exon 53 recited in the claims. These AOs had the same backbone chemistry (2'OMePS) and same length (25-mers) and were tested using the same cell types and transfection agents. (EX1001, Figs. 16 and 17; EX1095, ¶¶147–148.) Figures 16 and 17 of the '092 patent show this direct comparison:

Figure 16

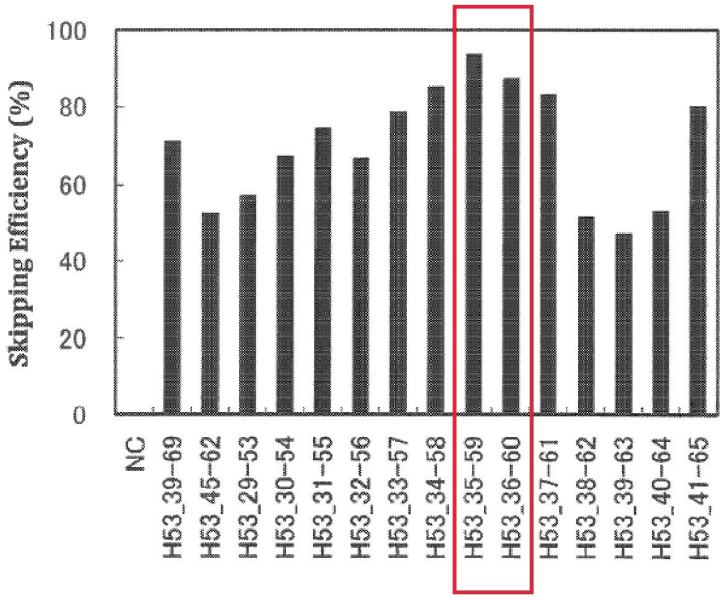
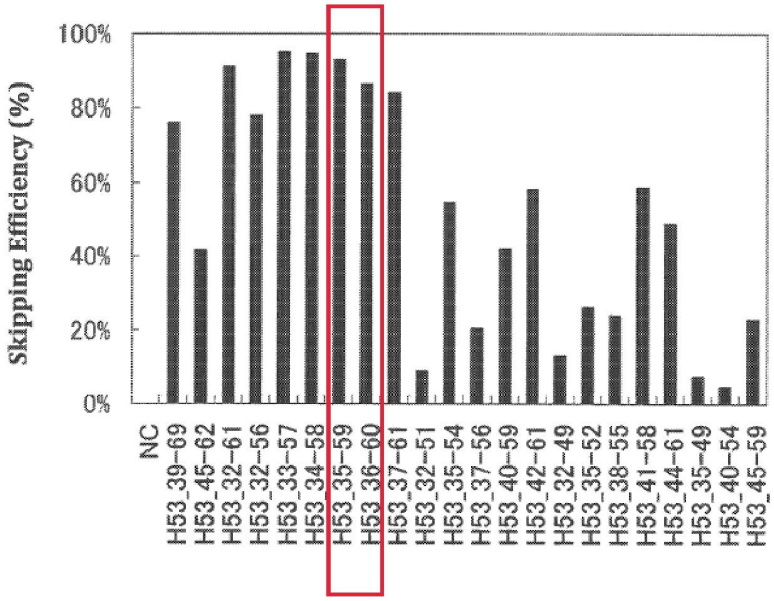


Figure 17



(EX1001, Figs. 16 and 17.)

This data further undermines NS's arguments of unexpected superiority. It reveals that AOs having the same target sequence as the challenged claims perform no better than, and perhaps less well than, an AO with the same target sequence as the closest prior art. (EX1095, ¶¶147–148.) *See, e.g.*, *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (unexpected results must be unexpected as compared with the closest prior art); *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) (same). Moreover, in a direct comparison in DMD patient cells, Popplewell teaches that PMO-A and PMO-G had similar exon skipping

efficacy. This data further calls into question the validity of NS's indirect comparison.[5] (EX1095, ¶¶149–151, 156.)

Finally, even if NS were to show some degree of increased efficacy for an AO targeting +36+60 as compared to the PMOs disclosed in Popplewell (which it has not), such a difference in degree would not have been unexpected and would not undercut a reasonable expectation of success for an AO targeting +36+60 (EX1095, ¶156). *See BMS*, 752 F.3d at 977 ("a mere difference in degree is insufficient" to render claimed subject matter patentable) (quotation marks omitted).

[5] NS made similarly deficient arguments during prosecution of the European counterpart patent of the '092 patent. (EX1095, ¶¶152-155.) There, NS submitted an "Experimental Report" (EX1084), which *indirectly* compared two AOs—a 25-mer AO targeting +36+60 and a 30-mer AO targeting the same sequence as PMO-H (+33+62) taught in Popplewell. (*Id.*) No direct comparison between the two AOs was provided. (*Id.*) Likewise, none of the tested AOs were compared against an AO targeting the same sequence as PMO-A (+35+59) taught in Popplewell. (*Id.*) As above, the *direct* comparison in Figures 16 and 17 calls into question the validity of NS's indirect comparison, particularly given that Popplewell teaches that PMO-A and PMO-H had similar exon skipping efficacy in DMD patient cells. (*Id.*)

Petitioner is not aware of any other alleged secondary considerations in support of nonobviousness and reserves the right to rebut any evidence NS submits.

2. Near-Simultaneous Development Precludes a Holding of Nonobviousness

In this case, the near-simultaneous development by others of an AO targeting the +36+60 sequence of exon 53 is objective evidence of obviousness. *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1376, 1389 (Fed. Cir. 2000); *Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010) ("Independently made, simultaneous inventions, made 'within a comparatively short space of time,' are persuasive evidence that the claimed apparatus 'was the product only of ordinary mechanical or engineering skill.'").

Within five months of NS's filing of its PCT application, researchers associated with Prosensa filed a provisional application on January 27, 2012, describing exon skipping AOs, including PMOs targeting exon 53. (EX1066, 1, 9–11, 58; EX1095, ¶¶157–158, 162–163.) Table 1 of the Prosensa application lists the following AO (SEQ ID NO: 52) targeting the +36+60 sequence of exon 53:

GYYGXXYXXGGYYXYGZZGGYGYYX

(EX1066, 58; EX1095, ¶159.) The application states that "X" equals cytosine or a modified form of cytosine called 5-methylated cytosine, "Y" equals uracil or a

modified form of uracil called 5-methylated uracil (i.e., thymine), and "Z" is either adenine (A) or 2-aminoadenine (a^2A). (EX1066, 56; EX1095, ¶160.)

When "X" equals cytosine, "Y" equals thymine, and "Z" equals adenine in SEQ ID NO: 52, as taught in the Prosensa application, a PMO of SEQ ID NO: 52 in the Prosensa application is 100% complementary to the +36+60 sequence of exon 53, the same target sequence as the PMOs recited in claims 1–3 of the '092 patent. (*Supra* § V.A; EX1095, ¶161.) This near simultaneous development is objective evidence of obviousness. (EX1095, ¶164.)

IX. The Same or Substantially the Same Arguments and Evidence Were Not Previously Presented to the Office

The arguments and evidence presented herein were not before the Office during examination of the '092 patent (or any related patent). Moreover, the Office made material errors in evaluating the prior art by overlooking teachings of Popplewell relevant to the patentability of the challenged claims, and in not considering Sazani, a new reference with relevant disclosures not cumulative to the prior art of record. This Petition also explains flaws in NS's unexpected results arguments made during prosecution of the grandparent '361 patent. Under *Becton Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential), the Board's November 2019 Trial Practice

Guide,[6] and *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 6–22 (PTAB Feb. 13, 2020) (precedential), the Board should not exercise its discretion under § 325(d).

First, there are material differences relevant to the patentability of the challenged claims between the asserted art and the prior art that formed the basis of rejections during prosecution of the grandparent '361 patent. *See Becton Dickinson*, IPR2017-01586, Paper 8 at 17 (factors (a) (b), and (c)). Petitioner's Ground 1 relies on Popplewell, a reference that was not relied upon during prosecution, in combination with Sazani, a reference that was not of record and is not cumulative to references considered by the Office during prosecution. Moreover, while the '092 patent incorrectly alleges that Popplewell does not disclose a technique for skipping with "high efficiency" (Ex. 1001, 2:51–56), this is contrary to its actual teachings and the published results described herein and in the declaration of Dr. Corey. *See Advanced Bionics*, IPR2019-01469, Paper 6 at 10 ("[I]f the record of the Office's previous consideration of the art is not well developed or silent, then a petitioner may show the Office erred by overlooking something persuasive under factors (e) and (f)."); *Navistar, Inc. v. Fatigue Fracture Tech.*, LLC, IPR2018-00853, Paper 13 at 16–17 (PTAB Sept. 12, 2018) ("[T]he fact that [references] were of record, but

[6] Consolidated Trial Practice Guide, 84 Fed. Reg. 64,280 (November 2019), 61–63.

not applied in any rejection by the Examiner . . . provides little impetus for us to exercise our discretion" under § 325(d).); *Abbott Vascular, Inc. v. FlexStent, LLC*, IPR2019-00882, Paper 11 at 23–25 (PTAB Oct. 7, 2019) (factors (a)–(d) weighed against denying the petition because "[t]he art relied upon by Petitioner . . . provides significant teachings that were not contained in the reference that the Examiner relied upon in a rejection").

Although Popplewell reports on results from the same study as the '212 Publication, Popplewell contains the complete results of the study, including critical disclosures not found in the '212 Publication regarding PMO-A (+35+59), the closest prior art AO to the claimed AOs targeting the +36+60 sequence of exon 53. In particular, in Popplewell, the authors conclude that the 25-mer PMO-A (+35+59) is a "viable alternative[]" to PMO-G as a clinical candidate. (*Supra* at § VI.D.) This contrasts with the '212 Publication (the basis of the Office's rejections during prosecution of the grandparent '361 patent), which expressed a preference for the 30-mer PMO-G (+30+59) and did not highlight any other PMO as a candidate for future clinical studies. *See Abbott Vascular*, Paper 11 at 23–25 (declining to deny institution and noting that "the specific arguments presented by Petitioner are substantively different than reasoning used by the Examiner").

This Petition explains that the Office erred in allowing the claims of the '092 patent in view of Popplewell, which teaches PMO-A (+35+59), a PMO the same

length as and targeting a sequence within exon 53 shifted just one nucleotide from the PMOs recited in the claims of the '092 patent. Based on the efficacy of PMO-A reported in Popplewell, the suggestion that PMO-A was a viable clinical candidate, and the pre-clinical information and chemical structure disclosed in Sazani (which was not of record), a POSA would have been motivated with a reasonable expectation of success to practice the claimed subject matter. Expert testimony by Dr. Corey, unavailable during prosecution, confirms these critical points. (EX1095, ¶¶1–9, 11–20, 94, 107–112, 116, 119–120, 124–130.) *See Becton Dickinson*, IPR2017-01586, Paper 8 at 18 (factors (d), (e), and (f)); *Advanced Bionics*, IPR2019-01469, Paper 6 at 8, n.9 ("[M]aterial error may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims.").

In addition, unlike the prior art of record, Sazani discloses the complete structure of AVI-4658 (the prior art exon skipping PMO in clinical trials for the treatment of DMD) including the TEG moiety conjugated at the 5'-end of the PMO—the same 5'-conjugated TEG moiety recited in claim 3 of the '092 patent. (EX1022, 145). Sazani further provides animal safety data that were "crucial in enabling [a clinical] study and in demonstrating the safety of AVI-4658 and the PMO class of compounds in general." (*Id.*, 154.) Such data, not reported in the prior art of record, would have been important for evaluating motivation to choose the AO

chemistry and 5'-moiety claimed by the '092 patent. *See Oticon Med. AB v. Cochlear Ltd.*, IPR2019-00975, Paper 15 at 19–20 (PTAB Oct. 16, 2019) (precedential) (failure to consider new, non-cumulative disclosures in a reference not submitted during prosecution constitutes an "error in [] prosecution").

This Petition also highlights flaws in NS's arguments during prosecution of the grandparent '361 patent, including NS's erroneous unexpected results arguments. *See Becton Dickinson*, IPR2017-01586, Paper 8 at 18 (factors (d), (e), and (f)). The Examiner's Notice of Allowance for the grandparent '361 patent, issued in reliance on NS's unexpected results argument, reveals that the Examiner overlooked that an AO targeting +36+60 displayed similar (and perhaps less) skipping efficacy than an AO targeting the same sequence as the closest prior art, PMO-A (+35+59). (*Supra* at § V.D.) This direct comparison was not addressed by either the Office or applicant during prosecution. Instead, the applicant's arguments in the grandparent case of unexpected results with respect to PMO-G disclosed in the '212 Publication involved a flawed, indirect comparison of *separate* experiments conducted under *different* conditions using *different* reagents and AOs with *different* chemical backbones, 5'-modifications, and lengths. (EX1095, ¶145.) As Dr. Corey explained, these differences—and other deficiencies of the experiments—make it difficult to assess the effect (if any) of AO target regions on skipping efficiency, undermining NS's alleged unexpected results arguments. (*Id.*) *See Becton Dickinson*,

IPR2017-01586, Paper 8 at 18 (factors (d), (e), and (f)); *Prollenium US Inc. v. Allergan Indus., SAS*, IPR2019-01617, Paper 17 at 53–61 (PTAB Mar. 20, 2020) (declining to exercise discretion under Section 325(d) in view of an expert declaration explaining defects in evidence of the alleged unexpected results submitted during prosecution); *Abbott Vascular*, IPR2019-00882, Paper 11 at 26–27 (additional facts and evidence presented in Petition warranted reconsideration of Examiner's findings regarding unexpected results).

Thus, this Petition demonstrates that institution is appropriate under the *Becton Dickinson* factors and both prongs of *Advanced Bionics* because the Office erred in evaluating Popplewell and in not considering Sazani, a reference not of record with non-cumulative disclosures relevant to patentability. This Petition further demonstrates that the Office committed material errors in evaluating and relying on NS's unsupported arguments of unexpected results made during prosecution.

X. Mandatory Notices Under 37 C.F.R. § 42.8

A. Real Parties-in-Interest

Sarepta Therapeutics, Inc. is the real party-in-interest.

B. Related Matters

Petitioner is not aware of any judicial matter that would affect or be affected by a decision in this proceeding.

Petitioner is concurrently filing petitions for *inter partes* review of the related '361, '106, '461, '741, '217, and '322 patents.

C. Lead and Backup Counsel

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D. Service Information

Please send all correspondence to lead counsel at the address shown above. Petitioner consents to service by e-mail at the e-mail addresses identified in the table above.

XI. Payment of Fees

The required fees are submitted herewith in accordance with 37 C.F.R. §§ 42.103(a) and 42.15(a). If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 06-0916.

XII. Conclusion

Sarepta respectfully requests that the Board grant this Petition for *Inter Partes* Review, institute trial, and find claims 1–3 of the '092 patent unpatentable.

Respectfully submitted,

Date: June 21, 2021

By: /William B. Raich/
William B. Raich (Reg. No. 54,386)

CERTIFICATION OF COMPLIANCE

The undersigned hereby certifies that the foregoing Petition contains 12,322 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper and a hand counting of words in the figures.

By: /William B. Raich/
William B. Raich (Reg. No. 54,386)

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), the undersigned certifies that on June 21, 2021 a copy of the foregoing **Petition for *Inter Partes* Review, the associated power of attorney,** and **Exhibits 1001-1007, 1011-1012, 1021-1033, 1035-1060, 1062-1077, 1084-1086, 1088, and 1095** were served by FedEx on the correspondence address of record indicated in the Patent Office's public PAIR system for U.S. Patent No. 10,385,092:

Zhengyu Feng, Ph.D.
FAEGRE DRINKER BIDDLE & REATH LLP
1500 K Street, N.W.
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Date: June 21, 2021

By: /William Esper/
William Esper
Legal Assistant

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, LLP

EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

----------x

NIPPON SHINYAKU CO., LTD.,

Plaintiff,

-against- C.A. No: 21-1015(GBW)

SAREPTA THERAPEUTICS, INC.,

Defendant.

----------x

SAREPTA THERAPEUTICS, INC. and
THE UNIVERSITY of WESTERN AUSTRALIA
Defendant/Counter-Plaintiffs,

V.

NIPPON SHINYAKU CO. LTD. And

NS PHARMA. INC.,

Plaintiff/Counter-Defendants.

----------x

VIDEOTAPED DEPOSITION of the Defendant, SAREPTA THERAPEUTICS, INC. by JOSEPH ZENKUS, taken by the Plaintiff, pursuant to Notice, held at the law offices of Finnegan, Henderson, Farabow, Garrett & Dunner, LLP 2 Seaport Lane Boston Massachusetts 02210, on July 25, 2023, at 9:15 a.m., before a Notary Public of the State of New York.

****

[redacted]

A P P E A R A N C E S:

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BY: RYAN P. O'QUINN, Ph.D., ESQ.
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ALSO PRESENT:

GEOFFREY BASSETT-Videographer
AMG Reporting
JESSICA DRISCOLL-Inhouse Counsel for Sarepta

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EXHIBITS

(Exhibits retained by Reporter.)

THE VIDEOGRAPHER: Good morning, everyone. Today's date is July 25, 2023, and the time is 9:15 a.m. Eastern Standard Time, and we are on the record. You're here today for the video-recorded deposition of Joe Zenkus in the matter of Nippon Shinyaku Co., LT -- Limited vs. Sarepta Therapeutics, Incorporated. Is that correct?

My name is Geoffrey Bassett with AMG Reporting. And the court reporter today is Brooke Perry. At this time, I will ask counsel to introduce themselves for the record.

MS. VENEGAS: Krista Venegas with Morgan Lewis on behalf of Nippon Shinyaku and NS Pharma.

MR. O'QUINN: Ryan O'Quinn with Finnegan on behalf of Sarepta Therapeutics, the University of Western Australia, and the witness.

THE VIDEOGRAPHER: All right. At this time, I will hand it over to the court reporter.

J O S E P H Z E N K U S, the witness herein, having been first duly sworn by a Notary Public of the State of New York, was examined and testified as follows:

EXAMINATION BY

THE REPORTER: Please, state your name for the record.

THE WITNESS: Joseph Zenkus.

[redacted]

MS. VENEGAS: Good morning. And during the course of the day, Mike Sikora, also of Morgan Lewis, will be joining us. He's not present in the room at the moment, but he will be joining us.

EXAMINATION BY

MS. VENEGAS:

Q. Good morning.

A. Good morning.

Q. Thanks for joining us for your deposition today. I'm sure your counsel has given you some background about the deposition, but have you ever been deposed before?

A. No.

Q. Okay. You understand you're going to be giving answers to my questions under oath, right?

A. Yes.

Q. Okay. And if you don't understand a question that I ask, please let me know. Okay?

A. Sure.

Q. If you answer a question, I'm going to assume that you understood it.

A. Understood.

Q. From time to time, your counsel may object to my question. Unless he instructs you not to answer, then I will anticipate that you're going to provide an answer to me.

A. Sure.

Q. Understood?

A. Understood.

Q. Okay. From time to time, about every hour or so, we'll go ahead and take a break, but if you need a break before then, please let me know.

A. I will.

Q. And the only thing that we ask is, if there's a question pending, that you please answer that question before we take the break.

A. Sure.

Q. Okay. You said you've never been deposed before in any capacity; is that right?

A. That's correct.

Q. So your first time. Let me go ahead and show

you a couple of documents.

[redacted]

before?

[redacted]

[redacted]

MS. VENEGAS: Let's take a short break, and I'll see if I can streamline a few things to get to the end.

THE WITNESS: Okay. Good, because I have to go to the bathroom.

MS. VENEGAS: Okay. Good timing.

THE WITNESS: Good timing.

THE VIDEOGRAPHER: The time is now 5:32, and we're off the record.

(Whereupon, a short break was taken.)

THE VIDEOGRAPHER: The time is 5:43, and we're on the record.

MS. VENEGAS: I'm going to mark as the next exhibit in order, I believe Exhibit 17, an e-mail chain beginning with the Bates SRPT-VYDS-0223093.

(Whereupon, SRPT-VYDS-0223093-95 was marked as Exhibit 17, for identification, as of this date.)

[redacted]

[redacted]

MS. VENEGAS: I'm going to mark as Exhibit 18 an e-mail Bates number SRPT-VYDS-0223092.

(Whereupon, SRPT-VYDS-0223092 was marked as Exhibit 18, for identification, as of this date.)

[redacted]

[redacted]

MS. VENEGAS: And I'm going to mark the next exhibit in order another series of e-mails, so Exhibit 19, document beginning Bates number SRPT-VYDS-0223211.

(Whereupon, SRPT-VYDS-0223211-14 was marked as Exhibit 19, for identification, as of this date.)

THE WITNESS: Thanks.

[redacted]

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11 Q. Why -- what was your understanding as to why
12 Sarepta was compelled to file seven IPRs against the
13 seven NS Patents?

17 A. Sarepta believes that the subject matter in
18 those patents was unpatentable,

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MR. O'QUINN: I pass the witness.
MS. VENEGAS: No further questions.
THE VIDEOGRAPHER: All right. The time is now 6:35 p.m., and we are off the record. Thank you, everyone.
(Time Noted: 6:36 p.m.)

A C K N O W L E D G M E N T

STATE OF NEW YORK)
:ss
COUNTY OF)

I, JOSEPH ZENKUS, hereby certify that I have read the transcript of my testimony taken under oath in my deposition of the 25th day of July, 2023; that the transcript is a true, complete and correct record of my testimony, and that the answers on the record as given by me are true and correct.

_____
JOSEPH ZENKUS

Signed and subscribed to before me, this day of , 2023.

_____
Notary Public, State of New York

C E R T I F I C A T E

STATE OF NEW YORK)
) ss.:
COUNTY OF QUEENS)

I, BROOKE E. PERRY, a Notary Public within and for the State of New York, do hereby certify:

That JOSEPH ZENKUS, the witness whose deposition is hereinbefore set forth, was duly sworn by me and that such deposition is a true record of the testimony given by such witness.

I further certify that I am not related to any of the parties to this action by blood or marriage; and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 25th day of July, 2023.

Brooke E. Perry

BROOKE E. PERRY

ERRATA SHEET

CASE NAME: NIPPON SHINYAKU CO., LTD. V. SAREPTA THERAPEUTICS, INC.
DATE OF DEPOSITION: July 25, 2023
WITNESS'S NAME: JOSEPH ZENKUS

Page	LINE (S)	CHANGE	REASON

JOSEPH ZENKUS

SUBSCRIBED AND SWORN TO BEFORE ME
THIS ____ DAY OF _____, 20__.

_____ _____
(NOTARY PUBLIC) MY COMMISSION EXPIRES: --

EXHIBIT C

ORAL ORDER: Having reviewed Plaintiff EIS's submission (D.I. 638), and Wow Tech's response thereto (D.I. 652), regarding EIS's request for clarification of the scope of the Court's order denying EIS's Motion in Limine No. 2 (D.I. 633), IT IS HEREBY ORDERED that EIS's request for clarification is DENIED. The Court finds that EIS has failed to meet its burden of demonstrating that the risk of prejudice or jury confusion is substantially outweighed by the probative value of the results of the inter-partes review ("IPR") proceedings. Moreover, the Court finds that EIS has failed to proffer a tenable solution regarding the instances in which Wow Tech may use the results of the IPR proceedings challenging some of the Asserted Patents. See D.I. 638 at 2 (EIS rejecting the Court's suggestion of a limiting jury instruction related to the results of the IPRs). Accordingly, the Court will not disturb its denial of EIS's Motion in Limine No. 2 (D.I. 633). Nothing in this Order is intended to limit or preclude EIS's ability to make a timely, specific objection during trial if any instances occur where EIS contends that Wow Tech is misrepresenting, inter alia, the results of the IPRs or the prior art considered by the PTAB in reaching those results. ORDERED by Judge Gregory B. Williams on 9/8/23. (ntl) (Entered: 09/08/2023)

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH) **DEMAND FOR JURY TRIAL**
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC., Plaintiff/Counter Defendants.	

NIPPON SHINYAKU CO., LTD. AND NS PHARMA, INC.'S REPLY IN SUPPORT OF THEIR MOTION *IN LIMINE* NO. 3 TO PRECLUDE MENTION OF *INTER PARTES* REVIEW PROCEEDINGS INVOLVING THE NS PATENTS

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Krista V. Venegas (admitted *pro hac* vice)
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Attorneys for Plaintiff/Counterclaim Defendant Nippon Shinyaku Co., Ltd. and Counterclaim Defendant NS Pharma, Inc.

Dated: April 29, 2024

Sarepta acknowledges that the Federal Circuit found that Sarepta breached contractual obligations by filing the IPRs. Despite this, Sarepta hopes to benefit from its contractual breach by seeking to introduce those same wrongfully filed IPRs to confuse the jury. This is improper.

First, Sarepta claims that if the IPRs are not admitted it cannot rebut NS's charge of willfulness. Not so. Sarepta is free to rebut NS's willfulness claim through admissible evidence such as an opinion of counsel (if it had one), which Sarepta unpersuasively tries to liken to the improperly filed IPRs. What Sarepta should not be permitted to do is argue to the jury that the PTAB's institution decision demonstrates that Sarepta had a good faith belief in the invalidity of the NS Patents. This would confuse and mislead the jury because the PTAB's decision is based on a far lower standard than is applicable to invalidity in this case. *See* Opening MIL (collecting cases excluding such evidence). None of the cases Sarepta cites supports admitting IPR evidence here. Two courts recognized that allowing mention of "PTAB" or "IPR" would in fact be too prejudicial and ***precluded*** such explicit references. *See Boston Sci.*, 2023 WL 2411277, at *1; *Hillman Grp.*, 2021 WL 1248180, at *3. The *Finjan* court ***excluded*** evidence of non-completed IPRs involving the patent-in-suit. 2020 WL 13180008, at *10. Finally, the *EIS* case involved completed IPRs, a far cry from the wrongfully filed and withdrawn IPRs in this case. *See* Ex. C to Sarepta's Response.

Second, none of the cases Sarepta cites support that NS would open the door to IPR evidence simply by arguing Sarepta's prior art references are cumulative. *Dentsply* stands for the noncontroversial position that if one party can use evidence regarding the IPRs, the other party can also rely on such IPR evidence. 2020 WL 6392764, at *4-5. In *Andover Heathcare*, after ***excluding*** IPR evidence as unduly prejudicial, the court said it would reconsider if the patent challenger raised a factual dispute over whether the PTO ever considered a certain prior art reference. 2016 WL 6404111, at *2. Neither of these scenarios will arise here.

April 29, 2024

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

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